ID64 STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Cladribine tablets for the treatment of relapsing-remitting multiple sclerosis [ID64]

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CONTAINS ACADEMIC IN CONFIDENCE AND COMMERCIAL IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Cladribine tablets for the treatment of relapsing-remitting multiple sclerosis [ID64]

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All authors read and commented on draft versions of this report.

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LIST OF ABBREVIATIONS

ABN	Association of British Neurologists
AC	Appraisal Committee
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ARR	annualised relapse rate
AST	aspartate aminotransferase
BCMS	British Columbia Multiple Sclerosis
BNF	British National Formulary
BSC	best supportive care
CDP	confirmed disability progression
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CrI	credible interval
CS	company submission
CSR	clinical study report
DIC	deviance information criterion
DMF	dimethyl fumarate
DMT	disease-modifying therapy
ECG	electrocardiogram
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
EQ-5D	EuroQol-5 dimension
ERG	Evidence Review Group
FAD	Final Appraisal Determination
FDA	Food and Drug Administration
FE	fixed-effects
GA	glatiramer acetate
Gd+	gadolinium enhancing
H	high-dose cladribine tablets over 48 weeks
HBV	hepatitis B virus
HCV	hepatitis C virus
HDA	high disease activity
HR	hazard ratio
HRQoL	health-related quality of life
HSU	health state utility
ICER	incremental cost effectiveness ratio
IFN-β1a	interferon-β1a
IPE	iterative parameter estimation
ITT	intention-to-treat
JC virus	John Cunningham virus
K-M	Kaplan-Meier
KFS	Kurtzke Functional systems
L	low-dose cladribine tablets over 48 weeks
LCI	lower bound of 95% confidence interval
LOCF	last observation carried forward
LYs	life years
MCMC	Markov Chain Monte Carlo
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSQOL-54	multiple sclerosis quality of life-54
NEDA-3	no evidence of disease activity
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
ONS	Office for National Statistics
P	placebo

PAS	patient access scheme
PH	proportional hazards
PML	progressive multifocal leukoencephalopathy
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	patient-reported outcome
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	quality adjusted life year
RCT	randomised controlled trial
RE	random-effects
RES	rapidly-evolving severe
RF	relapse-free
RPDFTM	rank preserving structural failure time model
RR	rate ratio
RRMS	relapsing-remitting multiple sclerosis
SD	standard deviation
SAE	serious adverse event
SAP	statistical analysis plan
SF-36	36-Item Short Form Survey
SLR	systematic literature review
SmPC	summary of product characteristics
SOT	sub-optimally treated
SPMS	secondary progressive multiple sclerosis
STA	single technology appraisal
TA	technology appraisal
TEAE	treatment-emergent adverse event
TRAE	treatment-related adverse events
TSAP	trial statistical analysis plan
UCI	upper bound of 95% confidence interval
VAS	visual analogue scale
vs	versus

1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence has been submitted to NICE by Merck in support of the use of cladribine tablets (mavenclad®) for two subgroups of people with relapsing-remitting multiple sclerosis (RRMS), namely, rapidly-evolving severe (RES) and sub-optimally treated (SOT) patients.

1.2 Critique of the decision problem in the company submission

Population

The population described in the final scope issued by NICE is adults with RRMS. The company has provided clinical evidence for people with RRMS, people with high disease activity (HDA-RRMS) and people with RES-RRMS and SOT-RRMS; the latter three subgroups were post-hoc classifications of people in the CLARITY trial.

Intervention

In June 2017, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) issued a positive opinion recommending the use of cladribine tablets for adults with highly active relapsing MS as defined by clinical or imaging features; people with RES-RRMS and SOT-RRMS are included in the population with highly active relapsing MS.

Cladribine tablets are administered orally. The recommended cumulative dose of cladribine tablets is 3.5 mg/kg body weight over 2 years, administered as 1 treatment course of 1.75 mg/kg per year. Each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective year.

Comparators

The final scope issued by NICE sets out different comparators for (i) people with RRMS who have not had previous treatment, (ii) people with RRMS who have received previous treatment, (iii) people with RES-RRMS and (iv) people with highly active RRMS despite previous treatment (i.e., people with SOT-RRMS).

No evidence was provided in the company submission (CS) for people with RRMS who have not received previous treatment or for people with RRMS who have received previous treatment.

The company carried out network meta-analyses (NMAs) using data from four populations: people with RRMS, people with HDA-RRMS, RES-RRMS and SOT-RRMS. The company compared cladribine tablets with a range of disease-modifying treatments (DMTs) including alemtuzumab, natalizumab, fingolimod and daclizumab.

Outcomes

Direct evidence is available from the CLARITY trial for the outcomes of qualifying annualised relapse rate (ARR), severity of relapse, disability, adverse events (AEs) and health-related quality of life (HRQoL). Freedom from disease activity using the 'no evidence of disease activity' (NEDA-3) composite clinical outcome, time to 6-month confirmed disability progression (CDP) and proportion of people with 6-month CDP were evaluated retrospectively.

Other considerations

- No evidence has been provided in the CS for the people described in the subgroup section of the final scope issued by NICE
- A patient access scheme (PAS) application for cladribine tablets is not included in the CS
- The company has not presented a case for cladribine tablets to be assessed against the NICE End of Life criteria
- The company has not identified any equity or equality issues.

1.3 Summary of the clinical evidence submitted by the company

The company presents evidence for the clinical effectiveness of cladribine tablets from the CLARITY trial. The CLARITY trial was a randomised, double-blind, placebo-controlled, multicentre, phase III trial designed to investigate the use of cladribine tablets in people with RRMS.

Direct evidence

The results from the CLARITY trial show that treatment with cladribine tablets is associated with a statistically significant improvement in qualifying ARR compared to placebo in the intention-to-treat (ITT) population, HDA-RRMS and RES-RRMS subgroups but not in the SOT-RRMS subgroup.

For secondary outcomes relating to relapse, cladribine tablets are shown to have a numerical advantage over placebo; these advantages are statistically significant within the ITT population, HDA-RRMS and RES-RRMS subgroups but not in the SOT-RRMS subgroup.

For secondary outcomes relating to disability progression, cladribine tablets are shown to have a numerical advantage over placebo; these numerical advantages are statistically significant

within the ITT population and HDA-RRMS subgroup but not for the RES-RRMS and SOT-RRMS subgroups.

Results of the composite, post-hoc, efficacy outcome NEDA-3, defined as 'no evidence of disease activity', showed numerically and statistically significant advantages for cladribine tablets compared to placebo in the ITT population and in all three subgroups.

In the overall population of the CLARITY trial, the proportions of treatment-emergent AEs (TEAEs) were similar in the cladribine tablets arm and in the placebo arm (80.7% and 73.3% respectively). Consistent with the mechanism of action of cladribine tablets, substantially more patients in the cladribine tablets arm compared with patients in the placebo arm experienced lymphopenia (21.6% versus 1.8% respectively) and leukopenia (5.6% versus 0.7% respectively).

Indirect evidence

The results of the NMAs that were undertaken for the efficacy outcomes of interest (qualifying ARR, 3-month CDP at 24 months and 6-month CDP at 24 months) generally show numerical and/or statistically significant advantages for cladribine tablets compared to most comparators, except for alemtuzumab and natalizumab. For alemtuzumab and natalizumab, the NMA results generally show a numerical disadvantage for cladribine tablets. However, there were very limited data available for the key efficacy outcomes for the RES-RRMS and SOT-RRMS subgroups.

Results of an additional meta-regression with the aim of estimating the efficacy of relevant DMTs compared to placebo in the RES-RRMS and SOT-RRMS subgroups, predict that all comparators are less effective in the SOT-RRMS subgroup than in the RES-RRMS subgroup. Furthermore, due to the significant overlap in the credible intervals across all comparisons, no therapy statistically dominates in terms of efficacy in either subgroup.

1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted

Direct evidence

The CLARITY trial was of good quality and was well conducted; participant characteristics were balanced across the two trial arms and the pre-planned statistical methods used were generally appropriate.

The clinical effectiveness evidence presented within the CS is mainly based upon three subgroups that were defined post-hoc as they were not considered to be relevant at the time of the original analysis of the CLARITY trial data. In addition, three post-hoc outcomes (NEDA-

3, time to 6-month CDP and proportion of people with 6-month CDP) were presented within the CS which were not included in the original analyses of the CLARITY trial data. The ERG understands why the company defined subgroups and outcomes retrospectively, i.e., to allow comparisons with the comparators/populations specified in the final scope issued by NICE. However, the ERG notes that the sizes of the RES-RRMS (cladribine, n=50; placebo, n=41) and SOT-RRMS (cladribine, n=19; placebo n=32)) subgroups are small and it is therefore difficult to detect statistically significant differences in outcomes.

Indirect evidence

The ERG considers that the company's general approach to undertaking NMAs and meta-regression) were appropriate in terms of the trials and comparators included, the statistical methodology employed, the model selection criteria, the choice of most appropriate model, and the interpretation of results.

The results of the NMAs carried out by the company should be viewed with caution due to the paucity of data available for the key efficacy outcomes; particularly for alemtuzumab in the RES-RRMS and SOT-RRMS populations.

The company also performed a meta-regression with the aim of estimating the efficacy of relevant DMTs compared to placebo in the RES-RRMS and SOT-RRMS. However, in light of the company's stated objectives, the ERG is not convinced that the results of the meta-regression presented by the company are valid or if the application of this meta-regression approach is appropriate.

1.5 Summary of cost effectiveness evidence submitted by the company

The company developed a de novo model in Microsoft Excel to generate cost effectiveness evidence for the comparison of cladribine tablets versus other DMTs. Evidence has been generated for the RES-RRMS and SOT-RRMS subgroups and the choice of comparator DMT depends on whether patients are able to receive alemtuzumab. The comparators for patients with RES-RRMS who are able to receive alemtuzumab are alemtuzumab and natalizumab, otherwise the comparators are natalizumab and daclizumab. The comparators for patients with SOT-RRMS who are able to receive alemtuzumab are alemtuzumab and fingolimod, otherwise the comparators are fingolimod and daclizumab.

The company model is a simplified version of models used to inform previous NICE multiple sclerosis technology appraisals. The basic structure comprises 11 health states: 10 Expanded Disability Status Scale (EDSS) states and a single state for death from all causes. In each cycle period (1 year) the cohort is at risk of moving to a higher EDSS state, moving to a lower

EDSS state, remaining in the current EDSS state, or dying. This is referred to as the natural history model. Adjustments to this model are made to reflect the effect of treatment on patient experience (for example, relapse rates, effect of treatment on rate of progression between health states, waning of drug efficacy over time, discontinuation of treatment and HRQoL). The model time horizon is set at 50 years and the perspective is that of the UK NHS and Personal Social Services. Model outcomes have been measured in quality adjusted life years (QALYs), and both costs and QALYs have been discounted at an annual rate of 3.5%, as recommended by NICE.

Within the company model, patient experience is reflected using published data, data from the CLARITY and CLARITY-EXT trials, clinical advice, and results from the company's NMAs and meta-regression. Resource use and costs have been estimated using information from the CLARITY trial, published sources and advice from clinical experts. Full list prices have been used to represent the cost of all DMTs. The company is unaware of the patient access prices for daclizumab and fingolimod.

Using list prices, the company base case incremental cost effectiveness ratios (ICERs) for the comparisons of treatment with cladribine tablets versus all the comparator DMTs, for both the RES-RRMS and SOT-RRMS subgroups, show that treatment with cladribine tablets is dominant.

The company carried out a wide range of deterministic sensitivity analyses. Results show that incremental net health effects are most sensitive to variation in the effect of DMT on 6-month CDP. Other key drivers include the rate at which costs and outcomes are discounted, baseline risk, the adjustment factor applied to the natural history model to account for the faster EDSS progression of patients with RES-RRMS and treatment discontinuation.

The company undertook probabilistic sensitivity analyses to assess the uncertainty surrounding the parameter values used in the model. Results from these analyses support the company's base case results as, for each analysis, treatment with cladribine dominates all other DMTs.

1.6 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG considers that model outputs are of limited use to decision makers. The ERG's two major areas of concern are (i) uncertainty around the effectiveness of cladribine tablets (versus placebo, and versus all other DMTs considered by the company), and (ii) the inclusion of costs and benefits that are outwith the NICE reference case. Whilst changes to the model can

address the second of these issues, no data are available to address the uncertainty around clinical benefit.

Uncertainty around effectiveness

- The key limitations, in terms of generating cost effectiveness evidence on cladribine tablets from the CLARITY trial are:
    - Evidence has been generated using data from subgroups that have been defined post-hoc.
    - The sizes of the subgroup populations are very small, with only 50 and 19 patients receiving cladribine tablets in the RES-RRMS and SOT-RRMS subgroups respectively.
    - The only outcome used in the company model that suggests that treatment with cladribine tablets is statistically significantly superior to placebo is qualifying ARR for the RES-RRMS subgroup.
    - There is no statistically significant evidence for patients in the SOT-RRMS subgroup that treatment with cladribine tablets is superior to placebo in terms of qualifying ARR or 6-month CDP (the two effectiveness outcomes used in the economic model).
- Confidence/credible intervals from the NMAs and meta-regression for cladribine tables and the other DMTs are wide. Even if the ERG had no concerns about the NMA and meta-regression, assessment of comparative effectiveness of cladribine tablets versus other DMTs would be speculative.
- After 2 years, the modelling of waning of treatment effectiveness, treatment discontinuation rates and efficacy of re-exposure to cladribine tablets or alemtuzumab, all of which have significant impact on overall effectiveness of each DMT, are almost entirely based on assumptions.
- The model submitted by the company only considers a single line of treatment. However, the ERG recognises that data to populate a more realistic lifetime model that includes multiple lines of treatment are not currently available.

The NICE reference case

- The NICE reference case stipulates that outcomes should reflect all direct health effects, whether for patients or for other people. However, costs (in the form of lost income) and health benefits (in the form of disutility associated with EDSS states and progression) to carers are included in the company model. The ERG considers that carers' lost income is not a direct cost and that health benefits to carers cannot be considered to be direct health benefits from treatment with cladribine tablets and that, therefore, neither should have been included in the company model.

1.7 ERG commentary on the robustness of evidence submitted by the company

1.7.1 Strengths

Clinical evidence

- The CLARITY trial was of good quality and was well conducted
- Participant characteristics were balanced across the two trial arms and the pre-planned statistical methods used were generally appropriate
- The methodological approach to the NMAs was generally appropriate.

Cost effectiveness evidence

- The company economic model, whilst difficult to check fully, appeared to be well constructed and fit for purpose
- Substantial effort had been taken to identify parameter values for the model.

1.7.2 Weaknesses and areas of uncertainty

Clinical evidence

- The HDA-RRMS, RES-RRMS and SOT-RRMS subgroups and three outcomes (NEDA-3, time to 6-month CDP and people with 6-month CDP) presented within the CS were not included in the original statistical analysis plan for the CLARITY trial
- The subgroup analyses were based on a small number of people
- The results from the NMAs are limited by the paucity of data available for the key efficacy outcomes
- The ERG is not convinced that the results of the meta-regression presented by the company are valid or if the application of this meta-regression approach is appropriate.

Cost effectiveness evidence

- There is no statistically significant evidence of effectiveness of cladribine tablets compared to placebo for the SOT-RRMS subgroup to incorporate into the economic model
- For the RES-RRMS subgroup, no statistically significant evidence was presented that cladribine tablets affect 6-month CDP more than placebo. This is important as slowing disease progression is the single biggest driver of cost effectiveness for any DMT
- There is no robust statistically significant evidence that cladribine tablets are more effective at reducing qualifying ARR than any other DMT in the RES-RRMS subgroup
- Long-term efficacy for DMTs, their waning of effect, levels of treatment discontinuation, re-exposure rates and efficacy after re-exposure are essentially unknown
- Disutility values and the costs of informal carer were included in the model. The ERG considers that both of these are outside of the NICE reference case.

1.8 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG considers that given the inherent uncertainty of the effectiveness evidence for cladribine tablets versus placebo and other DMTs, no changes could be made to the company

model that would generate robust cost effectiveness results. However, the ERG considers that some modifications can be made to the model to address some of the concerns raised in the ERG critique. For RES-RRMS these changes are:

- Modifications to qualifying ARR and 6-month CDP parameter values for cladribine tablets, alemtuzumab and daclizumab
- Setting the waning of treatment effect for cladribine equal to other DMTs
- Removing carers disutility
- Using alternative costs for EDSS states used in previous submissions
- Stopping treatment discontinuation for natalizumab and daclizumab after 2 years except if a patient reaches EDSS state 7.

Applying these changes over a 50-year time horizon results in:

- Treatment with cladribine tablets becoming dominated by alemtuzumab
- Treatment with cladribine tablets no longer dominating natalizumab, costing less (-£133,754) than natalizumab but generating fewer QALYs (-1.650) with an ICER per QALY **lost** of £81,050
- Treatment with cladribine tablets no longer dominating daclizumab, costing less (-£87,566) than daclizumab but generating fewer QALYs (-1.362) with an ICER per QALY **lost** of £64,269.

For interventions that are less costly and less effective (in terms of QALYs gained) than a comparator, the ICERs relate to the amount of money saved for every QALY that is lost by using the intervention rather than the comparator. When this is the case, an intervention will be considered cost effective if the ICER generated is **above** the willingness to pay threshold rather than below it.

In the absence of statistically significant trial evidence to show that treatment with cladribine is more effective than placebo for patients with SOT-RRMS for either 6-month CDP or qualifying ARR, there is no robust basis for any cost effectiveness results produced by an economic model.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

Sections B.1.3.1 and B.1.3.2 of the company submission (CS)[1] include an overview of multiple sclerosis (MS) and a brief description of the effects of the disease on people with MS. Key points from these sections of the CS are included as bulleted items in Box 1. The Evidence Review Group (ERG) considers that these points are accurate but that they lack detail on the burden of MS to people, carers and society.

Box 1 Company overview of multiple sclerosis

- MS is the most common debilitating neurological disease among young adults.[2]
- Approximately 85% of people with MS initially present with relapsing-remitting multiple sclerosis (RRMS), which is characterised by periodic acute exacerbations of disease activity (relapses) followed by periods of remission.[3]
- Relapses in people with RRMS are unpredictable and are associated with inflammation and development of new focal lesions, followed by periods of remission, leading to partial or complete recovery.[3]
- Over time (typically 15-20 years following disease onset), most people with RRMS will enter a phase of progressive neurodegeneration, with or without periodic relapses, associated with the accumulation of permanent disability, termed secondary progressive MS (SPMS).[3-6] In most clinical contexts, SPMS is diagnosed retrospectively by a history of gradual worsening after an initial relapsing disease course, with or without acute exacerbations during the progressive course.
- Some people with RRMS experience a more aggressive disease course. These people can be categorised as having high disease activity RRMS (HDA-RRMS); the definition of HDA-RRMS is evolving. HDA-RRMS can be associated with a constellation of clinical and imaging activities, including those defined by the European Medicines Agency (EMA) specifically for two other treatments for MS, natalizumab [7] and fingolimod:[8]
  - failure to respond to an adequate course of at least one disease-modifying therapy (DMT), presenting with at least one relapse in the previous year while on therapy and at least nine T2-hyperintense lesions or at least one gadolinium-enhancing lesion, or
  - treatment naïve with at least two disabling relapses in the last 1 year and at least one gadolinium-enhancing lesion or significant increase in T2-lesion load
- The time course for disease progression in RRMS is variable. The time it takes to reach an Expanded Disability Status Scale (EDSS) score of 6, noted as disability requiring assistance to walk, is reported to range between 15 years and 32 years from disease onset although there are multiple factors that can impact the time course of disease progression in RRMS including the age of the individual at disease onset, the initial disease course, and frequency of relapses.[6]
- In addition to clinical symptoms, people with RRMS may present with subclinical disease activity, in particular plaque lesions in the brain detected by magnetic resonance imaging (MRI), which often occur during remission. These lesions are indicative of active inflammatory disease activity and may predict disability and MS prognosis.[9]

Source: CS, Section B.1.3.1, Section B.1.3.2

The ERG notes that the final scope issued by NICE[10] describes the symptoms experienced by people with MS. The symptoms experienced by people with MS vary and might include pain, disturbance to muscle tone including weakness or spasticity, chronic fatigue, unsteady gait, speech problems, incontinence, visual disturbance and cognitive impairment.

The final scope issued by NICE[10] describes the relapsing-remitting form of multiple sclerosis (RRMS). It is stated in the scope that RRMS is characterised by periods of remission (when

symptoms are mild or disappear altogether) followed by relapses (which may or may not result in residual disability). Some people with RRMS can progress to develop secondary progressive multiple sclerosis (SPMS).

2.2 Critique of company's overview of current service provision

The company presents a brief overview of the clinical care pathway in Sections B.1.3.2 and B.1.3.3 of the CS and provides details of the McDonald diagnostic criteria for MS in Table 5 of the CS.[11] The ERG considers that the overview of the clinical care pathway in the CS is largely accurate.

The ERG notes that there is no current cure for MS and that RRMS is managed using disease-modifying therapies (DMTs). The aim of treatment with DMTs is to reduce the frequency and severity of relapses.

The company reports that the Association of British Neurologists (ABN)[12] classifies DMTs into Category 1 (moderate efficacy and established safety profiles) and Category 2 DMTs (high efficacy and more complex safety profiles). The DMTs in each category are listed in the CS (CS, Figure 6), and reproduced here in Figure 1. The company does not know whether the ABN will designate cladribine tablets as a Category 1 or Category 2 DMT. The company suggests that a new category might be needed (CS, p24). Clinical advice to the ERG is that cladribine tablets are likely to be considered as a Category 2 drug.

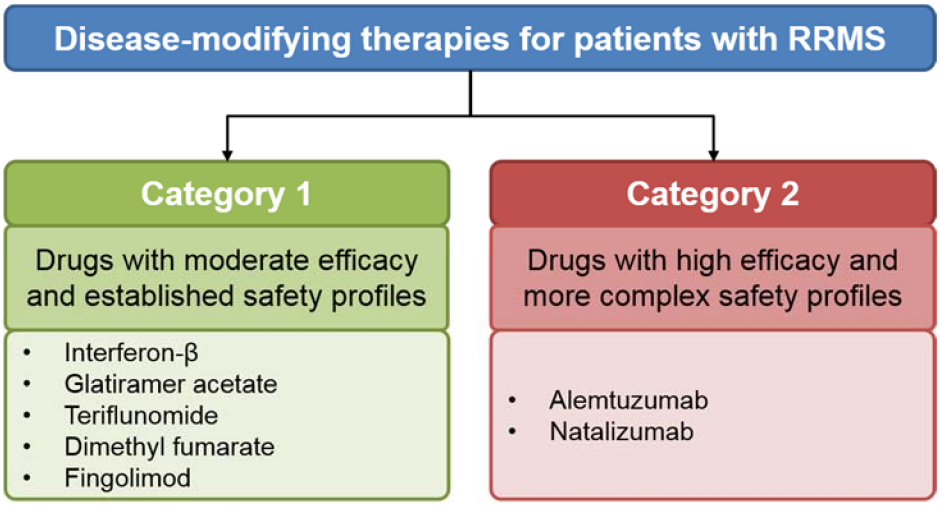

Figure 1 Categorisation of disease-modifying therapies according to the ABN guidelines

Source: CS, Figure 6

2.3 Indication / market authorisation

The company received a negative opinion in response to its 2009 marketing authorisation application to the European Medicines Agency (EMA)[13] for the treatment of people with RRMS

and to a subsequent application for conditional approval for the treatment of people with high disease activity RRMS (HDA-RRMS) in 2010 (CS, pp18-20). The company states that the Committee for Medicinal Products for Human Use (CHMP) acknowledged the efficacy benefits of treatment with cladribine tablets, but raised concerns about the safety profile (CS, p19). The company reports that the Food and Drug Administration (FDA) issued a complete response letter following the company's request in 2010 for conditional approval of the use of cladribine tablets to treat people with MS in the USA with HDA-RRMS.

A new marketing authorisation application was submitted to the EMA in June 2016 following the availability of new data (i.e. from the integrated safety analysis performed on combined data from the CLARITY, CLARITY-EXT and ORACLE trials, and the PREMIERE registry), which the company states 'has substantiated the positive clinical efficacy of cladribine tablets while also mitigating safety concerns previously identified by the CHMP' (CS, p20).

At the time the CS was submitted to NICE (26th June 2017), cladribine tablets did not have a marketing authorisation in Europe. The company had anticipated that the marketing authorisation for cladribine tablets would be for adults with HDA-RRMS (CS, p11). However, on the 22nd June 2017, the CHMP of the EMA[14] issued a positive opinion recommending the use of cladribine tablets for adults with highly active relapsing MS as defined by clinical or imaging features. The company states throughout the CS that they were assuming that the marketing authorisation granted by the EMA would be for the HDA-RRMS population, which includes people with rapidly-evolving severe RRMS (RES-RRMS) and people with RRMS sub-optimal therapy (SOT-RRMS). The HDA-RRMS is a narrower population than the highly active relapsing MS population.

2.4 Summary of relevant clinical guidance and guidelines

The CS does not include details of relevant published guidance and treatment guidelines for MS. A summary of the available NICE guidance for technologies included as comparators in the final scope issued by NICE is provided in Table 1.

The ERG notes that although beta interferon and glatiramer acetate are not currently recommended by NICE for the treatment of people with MS, these therapies are available in the NHS through a risk sharing scheme arranged by the Department of Health.[10] Beta interferon and glatiramer acetate are being assessed as part of an ongoing multiple technology appraisal (TA32).[15]

Table 1 Summary of NICE guidance for comparators inlcuded in the final scope issued by NICE

NICE guidance	Title	Recommendation
TA32[16] (2002) Update in progress	Beta interferon and glatiramer acetate for the treatment of multiple sclerosis	Neither beta interferon nor glatiramer acetate are recommended for the treatment of MS in the NHS in England and Wales.
TA127[17] (2007)	Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis	Natalizumab is recommended as an option for the treatment of RES MS. RES MS is defined as two or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous MRI.
TA254[17] (2012)	Fingolimod for the treatment of highly active relapsing–remitting multiple sclerosis	Fingolimod is recommended as an option for the treatment of highly active RRMS in adults, only if: • patients have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon, and • the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme.
TA303[17] (2013)	Teriflunomide for treating relapsing–remitting multiple sclerosis	Teriflunomide is recommended as an option for treating adults with active RRMS (normally defined as 2 clinically significant relapses in the previous 2 years), only if: • patients do not have highly active or RES-RRMS and • the manufacturer provides teriflunomide with the discount agreed in the patient access scheme.
TA320[18] (2014)	Dimethyl fumarate for treating relapsing‑remitting multiple sclerosis	Dimethyl fumarate is recommended as an option for treating adults with active RRMS (normally defined as 2 clinically significant relapses in the previous 2 years), only if: • patients do not have highly active RES-RRMS and • the manufacturer provides dimethyl fumarate with the discount agreed in the patient access scheme.
TA312[19] (2014)	Alemtuzumab for treating relapsing‑remitting multiple sclerosis	Alemtuzumab is recommended as an option, within its marketing authorisation, for treating adults with active RRMS.
TA441[20] (2017)	Daclizumab for treating relapsing–remitting multiple sclerosis	Daclizumab is recommended as an option for treating multiple sclerosis in adults, only if: • the person has active RRMS previously treated with disease-modifying therapy, or RES-RRMS (that is, at least 2 relapses in the previous year and at least 1 gadolinium-enhancing lesion at baseline MRI) and • alemtuzumab is contraindicated or otherwise unsuitable and • the company provides the drug with the discount agreed in the patient access scheme.
ID809[15] (in development)	Multiple sclerosis - interferon beta, glatiramer acetate (review TA32)	Publication date to be advised

MRI=magnetic resonance imaging; MS=multiple sclerosis; RES=rapidly-evolving severe; RRMS=relapsing–remitting multiple sclerosis; TA=technology appraisal

2.5 Innovation

The company puts forward the case that treatment with cladribine tablets is an innovative treatment (CS, section B.2.12). The company's case is set out in Box 2.

Box 2 Company's case for cladribine tablets as an innovative treatment

The key innovations for people with MS relate to the drug's posology:

- Short course, oral treatment: cladribine tablets require two short courses of oral treatment over 2 years, which could be self-administered at home, providing efficacy over a total of 4 years with no additional treatment required in years 3 and 4. This allows people with MS to be treated with minimal disturbance to their lives, with fewer medications to take and fewer hospital appointments compared with other DMTs.
- Monitoring burden: The contrast in monitoring requirements between cladribine tablets and other DMTs is significant and the impact on peoples' daily life is likely to be considerable. Six blood tests will be recommended for cladribine tablets during the first 2 years of treatment. Alemtuzumab, another annual treatment (for 2 years) for example, requires monthly blood monitoring.
- Fewer restrictions on family planning: MS typically affects young adults between the age of 20 and 40 years and twice as many women than men. People with MS receiving DMTs are recommended to stop treatment when they become pregnant, thereby increasing the risk of a relapse. Treatment with cladribine tablets allows people with MS to be treated in Year 1 and Year 2 with no further treatment in Year 3 and Year 4 and means that family planning can be considered from 6 months following the last dose of cladribine tablets in Year 2.
- Patient preference: The short course, oral nature of cladribine treatment was considered by the ABN as a potential motivator to some people with MS, preferred over the frequent monitoring burden and AEs associated with infusions, a comment that was reflected in the responses from the MS Society and MS Trust in the NICE scope consultations.
- In a Discrete Choice Experiment in the UK, people with MS considered that the attributes of cladribine tablets would provide [redacted] treatment options (overall) [redacted] treatment option in a future treatment landscape.

The key benefits for the healthcare system are financial, associated with the considerably lower administration and monitoring burden compared with other DMTs:

- Administration: Over the 4 years of cladribine tablets treatment, 20 days of oral dosing is required compared with 8 days of infusion for alemtuzumab, monthly infusions of natalizumab (approximately 48 over 4 years) and over 1,400 oral tablets where people with MS take one tablet per day.
- Monitoring: During their 2 years of treatment, people with MS receiving cladribine tablets will only require a total of six blood tests over 2 years (people with severe lymphopenia may require more tests) and monitoring for PML, which is a common opportunistic infection that can be fatal in people with weakened immune systems (although no case of PML has been reported to date with cladribine tablets). However, a baseline MRI should be performed before initiating cladribine tablets (usually within 3 months). In comparison, people with MS receiving natalizumab, fingolimod or alemtuzumab require multiple blood tests and additional analyses such as urinalysis, ophthalmological analyses, MRI and cardiovascular monitoring. The lower monitoring burden of people with MS treated with cladribine tablets compared with other DMTs results in lower monitoring costs over 4 years and increases the potential cost savings to NHS England.

ABN=Association of British Neurologists; AE=adverse event; DMT=disease-modifying therapy; MRI=magnetic resonance imaging; MS=multiple sclerosis; PML=progressive multifocal leukoencephalopathy
Source: CS, p78

Clinical advice to the ERG is that an oral MS treatment only given in two cycles that are 12 months apart, with no treatment in between or after, and with no unique monitoring above the standard, represents a step change and innovative treatment for people with MS.

2.6 Number of people with MS eligible for treatment with cladribine tablets

The company estimates that in England, the maximum number of people with MS who will be eligible for treatment with cladribine tablets ranges from 3983 people in 2017 to 4094 people with MS in 2021 (Table 2). The company claims that there are no data on the prevalence of HDA-RRMS in current UK clinical practice and has therefore estimated the proportion of people with HDA-RRMS eligible for treatment with cladribine tablets from the prevalence of HDA-RRMS in the population of the CLARITY trial (CS Budget Impact Analysis Section 3). The ERG considers this method to be appropriate since clinical advice to the ERG is that the incidence and prevalence of HDA-RRMS is unknown and participants included in the CLARITY trial are representative of people with MS likely to be treated in UK clinical practice. The company did not estimate the number of people in England with RES-RRMS and SOT-RRMS, i.e. the target populations for which cost effectiveness evidence was submitted by the company.

Table 2 Company's estimated incidence and prevalence of MS in England from 2017 to 2021

Epidemiology input	2017	2018	2019	2020	2021
Size of adult population in England[21]	42,523,609	42,857,169	43,170,266	43,456,282	43,717,703
Incidence rate of MS[22]	0.009%	0.009%	0.009%	0.009%	0.009%
Proportion of patients with RRMS - incidence[23]	77.0%	77.0%	77.0%	77.0%	77.0%
Prevalence rate of MS[22]	0.20%	0.20%	0.20%	0.20%	0.20%
Proportion of patients with RRMS - prevalence[24]	42.0%	42.0%	42.0%	42.0%	42.0%
Proportion eligible for treatment[25]	31.0%	31.0%	31.0%	31.0%	31.0%
Proportion with HDA-RRMS[26]	33.2%	33.2%	33.2%	33.2%	33.2%
Incidence of HDA-RRMS patients	306	309	311	313	315
Prevalence of HDA-RRMS patients	3676	3705	3732	3757	3780
Total population size	3983	4014	4043	4070	4094

HDA=high disease activity; MS=multiple sclerosis; RRMS=relapsing-remitting multiple sclerosis
Source: Adapted from the company's budget impact analysis submission, Table 7

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

A summary of the ERG's comparison of the decision problem outlined in the final scope issued by NICE[10] and that addressed within the CS is presented in

Table 3. Each parameter in

Final scope issued by NICE Parameter and specification	**Decision problem addressed in the company submission**
Final scope issued by NICE Parameter and specification	**Decision problem addressed in the company submission**
Population Adults with RRMS Intervention Cladribine tablets Comparators For people who have not had previous treatment • alemtuzumab • beta-interferon • daclizumab • dimethyl fumarate • glatiramer acetate • teriflunomide For people who have received previous treatment • alemtuzumab • daclizumab • dimethyl fumarate • teriflunomide For people with rapidly evolving severe RRMS • alemtuzumab • daclizumab • natalizumab For people with highly active RRMS despite previous treatment • alemtuzumab • daclizumab • fingolimod	Adults with RRMS with highly active disease (HDA-RRMS), in line with the anticipated marketing authorisation for cladribine tablets **Direct evidence** The CLARITY trial was designed to compare the clinical effectiveness of cladribine tablets vs placebo in people with RRMS. The company presented clinical data for the following populations: *For people with RRMS* Cladribine tablets vs placebo *For people with HDA-RRMS* Cladribine tablets vs placebo *For people with rapidly evolving severe RRMS (RES-RRMS)* Cladribine tablets vs placebo *For people with highly active RRMS despite previous treatment (also known as the sub-optimal therapy group) (SOT-RRMS)* Cladribine tablets vs placebo **Indirect evidence** The company used network meta-analysis and meta-regression to compare cladribine with relevant comparators as follows:

Table 3 is discussed in more detail in the text following the table (Section 3.1 to Section 3.6).

Final scope issued by NICE Parameter and specification	**Decision problem addressed in the company submission**

Population Adults with RRMS	Adults with RRMS with highly active disease (HDA-RRMS), in line with the anticipated marketing authorisation for cladribine tablets
Intervention Cladribine tablets	Cladribine tablets
Comparators For people who have not had previous treatment • alemtuzumab • beta-interferon • daclizumab • dimethyl fumarate • glatiramer acetate • teriflunomide For people who have received previous treatment • alemtuzumab • daclizumab • dimethyl fumarate • teriflunomide For people with rapidly evolving severe RRMS • alemtuzumab • daclizumab • natalizumab For people with highly active RRMS despite previous treatment • alemtuzumab • daclizumab • fingolimod	**Direct evidence** The CLARITY trial was designed to compare the clinical effectiveness of cladribine tablets vs placebo in people with RRMS. The company presented clinical data for the following populations: *For people with RRMS* Cladribine tablets vs placebo *For people with HDA-RRMS* Cladribine tablets vs placebo *For people with rapidly evolving severe RRMS (RES-RRMS)* Cladribine tablets vs placebo *For people with highly active RRMS despite previous treatment (also known as the sub-optimal therapy group) (SOT-RRMS)* Cladribine tablets vs placebo **Indirect evidence** The company used network meta-analysis and meta-regression to compare cladribine with relevant comparators as follows:

Table 3 Comparison between NICE scope and company decision problem

	For people with RRMS Cladribine tablets vs alemtuzumab Cladribine tablets vs beta-interferon Cladribine tablets vs daclizumab Cladribine tablets vs dimethyl fumarate Cladribine tablets vs glatiramer acetate Cladribine tablets vs teriflunomide Cladribine tablets vs fingolimod Cladribine tablets vs natalizumab *For people with HDA-RRMS* Cladribine tablets vs alemtuzumab Cladribine tablets vs beta-interferon Cladribine tablets vs dimethyl fumarate Cladribine tablets vs glatiramer acetate Cladribine tablets vs teriflunomide Cladribine tablets vs fingolimod Cladribine tablets vs natalizumab *For people with rapidly evolving severe RRMS (RES-RRMS)* Cladribine tablets vs alemtuzumab Cladribine tablets vs daclizumab Cladribine tablets vs natalizumab *For people with highly active RRMS despite previous* treatment (SOT-RRMS) Cladribine tablets vs alemtuzumab Cladribine tablets vs daclizumab Cladribine tablets vs fingolimod **No evidence** No evidence is presented in the CS for: For people with RRMS who have not had previous treatment For people with RRMS who have received previous treatment
Outcomes • relapse rate • severity of relapse • disability (for example EDSS) • symptoms of MS (such as fatigue, cognition and visual disturbance) • freedom from disease activity • mortality • AEs • HRQoL	The company presented results for the following outcomes: • qualifying annualised relapse rate • severity of relapse • disability (EDSS) • AEs • HRQoL • MRI lesions

Economic analysis The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY	Cost effectiveness was assessed using ICERs per QALY gained for the RES-RRMS and SOT-RRMS subpopulations
The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared	The model time horizon is 50 years
Costs will be considered from an NHS and Personal Social Services perspective	Costs have been considered from an NHS and Personal Social Services perspective
The availability of any patient access schemes (PAS) for the intervention or comparator technologies should be taken into account.	A PAS for cladribine tablets is not included in the CS
Other considerations If the evidence allows, the following subgroups of patients will be considered: • people with RRMS whose disease has inadequately responded to treatment with DMT • people with RRMS whose disease is intolerant to treatment with DMT • people with RRMS who are planning pregnancy	No evidence is presented in the CS for: • people with RRMS whose disease has inadequately responded to treatment with disease modifying therapy • people with RRMS whose disease is intolerant to treatment with disease modifying therapy • people with RRMS who are planning pregnancy
Special considerations None identified	None identified

AE=adverse event; CS=company submission; EDSS=Expanded Disability Status Scale; HDA=high disease activity; HRQoL=health-related quality of life; ICER=incremental cost effectiveness ratio; MRI=magnetic resonance imaging; N/A=not applicable; NEDA-3=no evidence of disease activity; NICE=National Institute for Health and Care Excellence; PAS=patient access scheme; QALY=quality adjusted life year; RES=rapidly evolving severe; RRMS=relapsing-remitting multiple sclerosis; SOT=sub-optimally treated; vs=versus
Source: CS, pp15-17

3.1 Population

The population specified in the final scope issued by NICE is adults with RRMS.

The clinical effectiveness evidence presented in the CS is derived from the CLARITY[27] trial which compared cladribine tablets to placebo. People were recruited to the CLARITY trial if they had a diagnosis of RRMS. Clinical effectiveness results for the overall trial population, the HDA-RRMS population, and subgroups of the HDA-RRMS population (i.e. RES-RRMS and SOT-RRMS) are provided in the CS. Only the RES-RRMS and SOT-RRMS subgroups are considered in the company's economic analyses.

The ERG notes that 28 people were recruited from the UK to the CLARITY trial. Clinical advice to the ERG is that the population included in the CLARITY trial is representative of people with MS likely to be treated in UK clinical practice. The company estimates that, from 2017, approximately 4000 people with HDA-RRMS in England would be eligible for treatment with

cladribine tablets each year (as discussed in Section 2.6 of the ERG report). Estimates of the incidence and prevalence of people in England and Wales with RES-RRMS and SOT-RRMS have not been provided in the CS.

It is recommended within the draft Summary of Product Characteristics (SmPC)[28] for cladribine tablets that they should be used with caution in the elderly as clinical studies have not included people with MS over 65 years of age; compared to younger persons, this age group is likely to have decreased hepatic or renal function, more concomitant diseases and use other treatments. In addition, the use of cladribine tablets has not been established, and therefore is not advised, in people with MS with moderate or severe renal or hepatic impairment.[28]

3.2 Intervention

The intervention described in the CS and in the final scope issued by NICE is cladribine tablets. The mechanism of action, method of administration and dosage of cladribine tablets is set out in Table 4.

Table 4 Mechanism of action, method of administration and dosage of cladribine tablets

Item	Description
Mechanism of action	Cladribine is a deaminase-resistant nucleoside analogue of deoxyadenosine that selectively depletes dividing and non-dividing T and B cells. The mechanism by which cladribine tablets exerts its therapeutic effects in MS is not fully elucidated but its predominant effect on B and T lymphocytes is thought to interrupt the cascade of immune events central to multiple sclerosis.[29] A distinguishing feature of cladribine tablets is discontinuous immunosuppression. Periods of lymphocyte depletion around treatment are followed by repopulation resulting in durable efficacy well beyond the period of treatment
Method of administration and dosage	Cladribine tablets are administered orally. The recommended cumulative dose of cladribine tablets is 3.5 mg/kg body weight over 2 years, administered as 1 treatment course of 1.75 mg/kg per year. Each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective year. Each treatment week consists of 4 or 5 days on which a person receives 10 mg or 20 mg (one or two tablets) as a single daily dose, depending on body weight. No further treatment is required in years 3 and 4

Source: CS, Table 3

The CS (p21) and the SmPC[28] include the caution that, due to the effect of treatment with cladribine tablets on lymphocytes, 'lymphocyte counts must be normal before cladribine tablets initiation in Year 1, and patients should have at least 800 cells/mm^3 before initiation of cladribine tablets in Year 2. In the absence of this, a treatment course could be delayed for up to 6 months to allow lymphocyte counts to recover.'

The effect of treatment with cladribine tablets on the immune system may result in an increase in the likelihood of infections. Screening for latent infections should be performed before initiation of therapy in year 1 and year 2 and patients should be monitored for signs and symptoms suggestive of any infection, with particular attention to herpes zoster.[28] The advice

in the SmPC[28] is that the initiation of cladribine tablets should be delayed until infections have been fully controlled.

The company claims that following completion of the two courses of treatment, no further treatment with cladribine tablets is required in years 3 and 4 (CS, p21). However, in the company's Budget Impact Analysis, the company estimates that 13.5% of patients would require a repeat course of cladribine tablets within the first 4 years of treatment initiation (CS Budget Impact Analysis, Table 1). The company's estimate was based on the proportion of participants who relapsed in the CLARITY-EXT trial.[30] The company states that re-initiation of cladribine tablets after year 4 has not been assessed (CS, p21).

3.3 Comparators

The final scope issued by NICE does not explicitly specify comparators for the whole adult population with RRMS. Instead, the final scope sets out different comparators for (i) people who have not had previous treatment, (ii) people who have received previous treatment, (iii) people with RES-RRMS and (iv) people with highly active RRMS despite previous treatment, which the company termed as SOT-RRMS.

No evidence was provided for people with RRMS who have not received previous treatment or for people with RRMS who have received previous treatment.

The CS includes network meta-analyses (NMAs) that include data from the RRMS population (i.e., CLARITY trial intention-to-treat [ITT] population) and data from the HDA-RRMS subpopulation; neither of these populations was part of the final scope issued by NICE.

Only the NMAs that included data from the RES-RRMS and SOT-RRMS populations match the populations and comparators set out in the final scope issued by NICE (Table 5). However, the RES-RRMS and SOT-RRMS subgroups and efficacy and safety analyses were not pre-specified in the CLARITY trial statistical analysis plan (SAP). All of the efficacy analyses are based on data from a small number of people.

Table 5 Comparators listed in the final scope for which the company presented indirect clinical evidence

Population	Definition	Comparators
RES-RRMS	People with 2 or more relapses in prior year whether on treatment or not, and at least 1 T1Gd+ lesion	Natalizumab Alemtuzumab Daclizumab
SOT-RRMS	People with 1 or more relapse in the prior year while on DMT and at least 1 T1Gd+ lesion or 9 T2 lesions	Fingolimod Alemtuzumab Daclizumab

DMT=disease modifying therapy; Gd+=gadolinium enhancing; RES=rapidly-evolving severe; RRMS=relapsing-remitting multiple sclerosis; SOT=sub-optimally treated

Source: adapted from CS, Table 62

3.4 Outcomes

The outcomes specified in the final scope issued by NICE and considered in the CS are qualifying annualised relapse rate [ARR]), severity of relapse, disability, AEs and health-related quality of life (HRQoL). In addition, the company included magnetic resonance imaging (MRI) lesions, explaining that clinicians commonly use MRI results to assist in the diagnosis and prognosis of RRMS. Freedom from disease activity was evaluated post-hoc using the 'no evidence of disease activity' (NEDA-3) composite clinical outcome defined as no relapses, no 3-month confirmed EDSS progression, no new or enhancing T1 gadolinium enhancing (Gd+) lesions and no new or enlarging T2 lesions. Time to 6-month confirmed disability progression (CDP) and people with 6-month CDP were also evaluated retrospectively. Clinical advice to the ERG is that NEDA-3 and CDP scores have not been validated as predictors of long term outcome. Symptoms of MS (such as fatigue, cognition and visual disturbance) was a specified outcome in the final scope issued by NICE but was not addressed in the CS. Clinical advice to the ERG is that symptoms of MS as specified in the final scope issued by NICE were not commonly reported at the time when the CLARITY trial was designed.

3.5 Economic analysis

As specified in the final scope issued by NICE, the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained for the RES-RRMS and SOT-RRMS subgroups. Outcomes were assessed over a 50-year time period (equivalent to a lifetime horizon) and costs were considered from an NHS and Personal Social Services (PSS) perspective. The company subdivided the RES-RRMS and SOT-RRMS subgroups as described in Table 6.

Table 6 Summary of populations and comparators considered in the CS for the economic analysis

Population	Definition	Comparators within scope
RES-RRMSa	RES-RRMS and able to receive alemtuzumab	Natalizumab Alemtuzumab
RES-RRMSb	RES-RRMS and either contraindicated or otherwise unable to receive alemtuzumab	Natalizumab Daclizumab
SOT-RRMSa	SOT-RRMS and able to receive alemtuzumab	Fingolimod Alemtuzumab
SOT-RRMSb	SOT-RRMS and either contraindicated or otherwise unable to receive alemtuzumab	Fingolimod Daclizumab

RES=rapidly evolving severe; RRMS=relapsing-remitting multiple sclerosis; SOT=sub-optimally treated
Source: adapted from CS, Table 62

The company states that these subdivisions were necessary to align the results of the current appraisal with the recommendation set out in the Final Appraisal Determination (FAD) for daclizumab (TA441).[20] Daclizumab is recommended as a treatment for people with RES-RRMS and SOT-RRMS and for whom alemtuzumab is contraindicated or unsuitable. Daclizumab is therefore a relevant comparator to cladribine tablets in people with RES-RRMS and SOT-RRMS who are unable to receive alemtuzumab. The ERG agrees that the approach employed by the company is appropriate. However, the subgroup analyses were not pre-specified and the analyses are based on small number of participants.

3.6 Other considerations

No evidence has been provided in the CS for the subgroups specified in the NICE scope, specifically, for people with RRMS whose disease has inadequately responded to treatment with a DMT, for people with RRMS for whom treatment with a DMT is not suitable because of intolerance or contraindication, and patients with RRMS who are planning pregnancy.

The company did not identify any equity or equality issues.

The company states that a patient access scheme (PAS) application for cladribine tablets is not included in the CS (CS, Table 3). The ERG notes that fingolimod and daclizumab are both available to the NHS at discounted PAS prices. PAS prices are confidential and therefore not known to the company. The ERG has re-run the company's base case analyses using the discounted PAS prices (see Confidential Appendix to this ERG report for results).

4 CLINICAL EFFECTIVENESS

4.1 Critique of the review methods

4.1.1 Searches

The company carried out a systematic search of the literature in January 2017 to identify randomised controlled trials (RCTs) investigating the efficacy and safety of cladribine tablets for the treatment of people with RRMS. Separate searches were conducted for the retrieval of cost effectiveness studies, HRQoL studies and 'health state unit cost and resources' studies. The searches were conducted in February 2016 and updated in January 2017.

Full details of the searches and the strategies used to locate clinical evidence are reported in Section B.2.1 and Appendix D of the CS. There are some syntax errors with regards to the translation of the search strategies between databases, for example, the PubMed interface does not use NEAR, therefore any search lines using NEAR do not execute correctly in the PubMed Interface. The company has not translated the searches consistently between databases; the search terms for the disease that was used for the Medline and Embase searches are not the same as the search terms used in The Cochrane Library and PubMed searches. However, the ERG considers that these errors are unlikely to have resulted in any papers being missed due to the search terms still being relevant and comprehensive. No clinical trial registries were searched by the company, which could have resulted in some relevant ongoing trials being missed. The ERG updated the company searches for the period between January and July 2017 and is satisfied that no relevant studies have been missed.

The ERG considers that the company's searches were carried out to an adequate standard, however, they could have been executed more consistently. The searches accurately reflected the population and indication described in the final scope issued by NICE.

The data sources searched and the time spans for the searches are provided in Table 7. A summary of, and ERG comments on, the review methods used by the company are presented in Table 8.

Table 7 Data sources for the clinical systematic review

Search strategy component	Source	Search date range	
		Start	End
Electronic database searches	EMBASE	Not specified, possibly from database inception	February 2016, updated January 2017
	MEDLINE		
	MEDLINE In-Process		
	Cochrane Central Library of Controlled Trials (CENTRAL)		
Congress proceedings	Academy of Managed Care Pharmacy (AMCP) (Biannual meeting) American Academy of Neurology (AAN) (Annual meeting) American Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) (Annual meeting) American Neurological Association (ANA) (Annual meeting) Consortium of Multiple Sclerosis Centers (CMSC) (Annual meeting) European Academy of Neurology (EAN) (Annual meeting)* European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) (Annual meeting) European Federation of Neurological Societies (EFNS) International Society of Pharmacoeconomics and Outcomes Research (ISPOR)	2012	February 2016, updated January 2017
Clinical trial registries	ClinicalTrials.gov	Not searched	
	WHO's meta-registry 'International Clinical Trials Registry Platform Search Portal' (ICTRP)		
	EU Clinical Trial Registry		

Source: CS, Appendix D, Table 5 and Table 6

Table 8 Summary of, and ERG comment on, the systematic review methods used by the company

Review method	Results	ERG comment
Searching		
Sources searched: • Electronic databases • Congress proceedings • Clinical trial registries	10,825 unique studies	• The last update was carried out in January 2017 meaning that there is a risk that some relevant studies may not have been included in the search results • There are some syntax errors with regards to the translation of the search strategies between databases meaning that some searches would not execute correctly • Clinical trial registries were not searched. Ongoing clinical trials were therefore not identified in the CS
Formal eligibility criteria		
Two analysts independently assessed study eligibility based on the criteria presented in Table 7 of Appendix D of the CS (pp15-16)	49 unique trials based on 779 publications and 2 CSRs	• Use of two independent assessors improves the quality of the review
Additional eligibility criteria		
Search limits		It is unclear if the searches were restricted to studies published in English language. However, the legend in PRISMA flow diagram indicates that non-English studies were excluded. Relevant non-English language studies may not have been included
Quality assessment		
The company assessed the risk of bias of the CLARITY trial using the minimum criteria recommended by NICE.[31] The results of the company assessment of the CLARITY trial are presented in the CS The company assessed the risk of bias of the RCTs included in company's NMA using the Jadad score[32] and the minimum criteria recommended by NICE.[31] The results of the company's assessment of risk of bias of the RCTs included in the company's NMA are presented in an embedded file in Appendix D of the CS		

CS=company submission; CSR=clinical study report; ERG=Evidence Review Group; NMA=network meta-analysis; PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT=randomised controlled trial
Source: CS, Appendix D Table 7

4.1.2 Evidence synthesis

The company presents direct evidence to support the clinical efficacy of cladribine tablets from one RCT (the CLARITY trial). The CS includes a narrative description of this trial.

4.2 ERG critique of direct clinical effectiveness evidence

4.2.1 Identified trials

Key trial: the CLARITY trial

The company presents evidence for the clinical effectiveness of cladribine tablets from the CLARITY trial. The CLARITY trial was a randomised, double-blind, placebo-controlled, multicentre, phase III trial designed to investigate the use of cladribine tablets in people with RRMS.

Other trials

Neither the company nor the ERG identified any trials that directly compare cladribine tablets with any of the comparators listed in the final scope issued by NICE.

Data from the CLARITY-EXT trial were included in the CS to provide supportive evidence for the assumptions about the waning of the effect of cladribine tablets that are used in the company's economic model and safety. Waning assumptions used in the company model are further discussed in Section 5.3.6 of this report.

Safety data extracted from the PREMIERE registry[33] and ORACLE trial[34] were used, in addition to safety data from the CLARITY and CLARITY-EXT trials, as part of an integrated safety analysis. The PREMIERE registry[33] collects safety data on patients that received a 3.5 mg/kg dose of cladribine tablets as part of any RCT. The ORACLE trial[34] assessed the effect of cladribine tablets at a cumulative dose of 3.5 mg/kg or 5.25 mg/kg over 96 weeks versus placebo in patients who experienced a single, first clinical event suggestive of MS. The patient population in the ORACLE trial[34] does not match the patient population(s) specified in the final scope issued by NICE.

4.2.2 Key characteristics of the CLARITY trial

The key characteristics of the CLARITY trial are provided in the CS (Section B.2.3) and are summarised in Table 9.

The trial was conducted internationally, with six treatment centres located in the UK. Patients were randomised 1:1:1 to receive either low-dose cladribine tablets 3.5 mg/kg cumulative (n=433), high-dose cladribine tablets 5.25 mg/kg cumulative (n=456) or placebo (n=437) over a period of 96 weeks. The CLARITY trial was divided into two 48-week treatment periods (year 1 and year 2) with four 28-day treatment cycles in year 1 (week 1, week 5, week 9, week 12) and two 28-day treatment cycles in year 2 (week 48 and week 52). Cladribine tablets were given as 0.875 mg/kg/cycle with the number of tablets administered being standardised based on weight. People allocated to receive cladribine tablets 3.5 mg/kg cumulative, were given cladribine tablets in week 1, week 5, week 48 and week 52 and placebo in week 9 and week 12. People allocated to receive cladribine tablets 5.25 mg/kg cumulative were given cladribine tablets in all treatment cycles and people allocated to placebo were given placebo in all cycles.

The company states that results from the CLARITY trial demonstrated 'no considerable differences' in the efficacy and safety of 3.5 mg/kg cladribine tablets compared to 5.25 mg/kg cladribine tablets[27] and so the 5.25 mg/kg cladribine tablets dose was omitted from the CLARITY-EXT trial.[35] Furthermore, 3.5 mg/kg is the anticipated EMA licensed dose for

cladribine tablets. Therefore, only results for the 3.5 mg/kg cladribine tablets treatment arm (compared to the placebo treatment arm) are presented within the CS and only the 3.5 mg/kg cladribine tablets and placebo arm data contribute to the NMA and to the economic evaluation. For these reasons, all subsequent mentions of treatment with cladribine tablets in this ERG report refer to a 3.5 mg/kg dose.

The CLARITY trial had pre-planned subgroup analysis of active RRMS patients grouped into treatment-naïve RRMS and treatment-experienced RRMS. The company states that the results of these subgroups were not included in the CS as they did not expect that cladribine tablets would obtain marketing authorisation for these populations.

Table 9 Key characteristics of the CLARITY trial

Trial	**CLARITY**
Trial design	Phase III double-blind, parallel group, placebo-controlled, multicentre, 96-week
Eligibility criteria for participants	Diagnosis of MS according to the McDonald criteria RRMS with ≥1 relapses within 12 months before study Clinically stable and not had a relapse within 28 days prior to day 1 of study MRI lesions consistent with MS at the pre-study evaluation according to the Fazekas criteria EDSS score between 0 to 5.5, inclusive
Settings and locations where the data were collected	155 investigative sites in 32 countries (28 patients in 6 sites across the UK)
Trial drugs - Interventions and comparators	Patients (N=1326) were randomised (1:1:1) to receive: LL: cladribine tablets 3.5 mg/kg cumulative over 96 weeks (n=433) HL: cladribine tablets 5.25 mg/kg cumulative over 96 weeks (n=456) PP: placebo (n=437)
Trial drugs - permitted and disallowed concomitant medication	• Corticosteroids were permitted to treat acute relapses, however, long-term use (>14 days) necessitated patient withdrawal from the trial • IFN-β1a (Rebif) was permitted as rescue medication after 24 weeks from the start of the trial – to qualify for Rebif rescue medication, patients had to meet the following criteria: ○ Patients who experience >1 qualifying relapse, and/or ○ Patients who have a sustained increase in their EDSS of ≥1 point (or ≥1.5 points if baseline EDSS was 0) over a period of 3 months or greater)
Primary outcomes (including scoring methods and timings of assessments)	Qualifying ARR – defined as a two grade increase in ≥1 KFS or a one grade increase in ≥2 KFS, excluding changes in bowel/bladder or cognition, in the absence of fever, lasting for ≥24 hours, and preceded by ≥30 days of clinical stability or improvement
Other outcomes used in the economic model/specified in the scope	Disability progression Mortality Adverse effects of treatment HRQoL NEDA-3 (post-hoc) 6-month CDP (post-hoc)

Pre-planned subgroups	Prior treatment Treatment-naïve Treatment-experienced
Post-hoc subgroups	HDA-RRMS (licensed population) RES-RRMS SOT-RRMS

ARR=annualised relapse rate; CDP=confirmed disease progression; EDSS=expanded disability status scale; H=high-dose cladribine tablets over 48 weeks; HDA=high disease activity; HRQoL=health-related quality of life; IFN-β1a=interferon-β1a; KFS=Kurtzke Functional systems; L=low-dose cladribine tablets over 48 weeks; MRI=magnetic resonance imaging; MS=multiple sclerosis; NEDA-3=no evidence of disease activity; P=placebo; RES=rapidly evolving severe; RRMS=relapsing-remitting multiple sclerosis; SOT=sub-optimally treated
Source: CS, Table 8

4.2.3 Characteristics of patients enrolled in the CLARITY trial

The key baseline characteristics of patients included in the CLARITY trial are presented in Table 10. The company considers that the patients' baseline characteristics are generally well-balanced, and that although there is a higher proportion of patients (≈5%) who had received previous DMT in the placebo group than in the cladribine tablets group, the difference is not statistically significant (CS, Section B.2.3.4). Disease duration from first onset was statistically significantly lower in the cladribine tablets 3.5 mg/kg group than in the placebo and cladribine tablets 5.25 mg/kg groups in the published paper. Mean disease duration reported in the CS for the placebo and cladribine groups is shorter than reported in the paper. In response to the ERG clarification letter, the company acknowledged these differences and explained that the differences were due to the different definitions used for disease duration. In the published paper,[27] the duration was defined as "the time (in years) from the first attack until randomisation", whereas for the results of the re-analyses presented in the CS, the duration was adapted to a more commonly used definition, "the time (in years) from the MS diagnosis date until randomisation".

Table 10 Baseline characteristics of patients in the CLARITY trial

Characteristic	**CLARITY**	
	Placebo (n=437)	**Cladribine tablets 3.5 mg/kg (n=433)**
Mean (SD) age, years	38.7 (9.9)	37.9 (10.3)
Female, %	65.9	68.8
Previous DMT use, %	30.2	25.4
Mean disease duration, years	5.2	4.7
Mean (SD) EDSS	2.9 (1.3)	2.8 (1.2)
Mean (SD) T1 Gd+ lesions	0.8 (2.1)	1.0 (2.7)
Mean (SD) T2 lesions	27.4 (17.7)	25.3 (16.3)

DMT=disease-modifying therapy; EDSS=expanded disability status scale; Gd+=gadolinium-enhancing; SD=standard deviation
Source: CS, Table 13

The CS also includes the baseline characteristics of the subgroups defined by the company (i.e., HDA-RRMS, RES-RRMS and SOT-RRMS). The baseline characteristics of these subgroups are presented in Table 11. The ERG notes that small numbers of people were

included in the RES-RRMS and the SOT-RRMS subgroups (see Table 11 for details). The ERG notes that some patients could be classified as RES-RRMS and/or SOT-RRMS and, according to the company during the clarification teleconference that was held with NICE and the ERG, some patients may have been included in both of these subgroups resulting in double counting.

The ERG notes that the HDA-RRMS subgroup is larger than the sum of the numbers of patients in the RES-RRMS and SOT-RRMS subgroups.

Table 11 Patients baseline characteristics in the CLARITY trial by subgroup

Characteristic	Placebo subgroups			Cladribine tablets 3.5 mg/kg subgroups		
	HDA-RRMS (n=149)	RES-RRMS (n=41)	SOT-RRMS (n=32)	HDA-RRMS (n=140)	RES-RRMS (n=50)	SOT-RRMS (n=19)
Mean (SD) age, years	37.1 (10.2)	33.3 (8.2)	38.0 (8.8)	36.3 (9.5)	33.4 (7.9)	34.7 (8.0)
Female, %	63.1	58.5	68.8	72.9	72.0	73.7
Previous DMT use, %	37.6	24.4	100.0	32.9	34.0	100.0
Mean disease duration, years	4.8	3.9	7.6	3.9	2.9	5.8
Mean (SD) EDSS	3.0 (1.4)	2.9 (1.4)	3.6 (1.6)	2.9 (1.3)	2.8 (1.4)	3.2 (1.5)
Mean (SD) T1 Gd+ lesions	1.0 (2.8)	3.5 (4.6)	1.2 (2.1)	1.3 (3.5)	3.6 (5.6)	0.5 (0.8)
Mean (SD) T2 lesions	29.9 (19.8)	36.8 (24.4)	35.7 (21.1)	25.2 (17.2)	31.6 (16.8)	26.6 (18.1)

DMT=disease-modifying therapy; EDSS=Expanded Disability Status Scale; Gd+=gadolinium-enhancing; HDA=high disease activity; RES=rapidly evolving severe; RRMS=relapsing-remitting multiple sclerosis; SD=standard deviation; SOT=sub-optimally treated
Source: CS, Table 14

4.2.4 Statistical approach adopted

In this section, the ERG provides a description and critique of the statistical approaches used to analyse data collected during the CLARITY trial that relate to the outcomes stipulated in the final scope issued by NICE. Information relevant to the statistical approach taken by the company has been extracted from the CSR,[36] the trial protocol,[37] the trial statistical analysis plan (TSAP)[38] and the CS, which included post-hoc subgroup analyses of the CLARITY trial.

The objective of the CLARITY-EXT trial was to evaluate safety of extended treatment with cladribine tablets and to provide supportive evidence for assumptions on waning used in the economic analysis rather than to evaluate efficacy. With the exception of waning assumptions, data from the CLARITY-EXT trial were not used to populate the submitted economic model. Waning assumptions are further discussed in Section 5.3.6 of this ERG report. Therefore, the methodology and the statistical approach of the CLARITY-EXT trial are not discussed within this ERG report but can be found in Section B.2.3 and Section B.2.4 of the CS respectively.

Analysis populations

The populations used for analyses of different outcomes of the CLARITY trial are summarised in Table 12. Data from the ITT population were analysed for all pre-planned primary and important secondary efficacy outcomes and data from the safety population were used in all safety analyses. The ERG notes that data from additional trials were combined with data from the CLARITY trial in an integrated safety analysis in the CS (Section B 2.10.3); further details of the safety population and analyses presented within the CS are described in Section 4.5 of this ERG report.

The ERG is satisfied that the populations for pre-planned outcomes were pre-defined in the TSAP (p85) and that all relevant results are reported within the CSR (p102-106).

The ERG notes that analyses of HRQoL are defined in the CLARITY protocol (pp 69-70) but the analysis population for these analyses is not defined in either the CLARITY trial protocol or in the TSAP. Information in the CSR for the CLARITY trial (requested by the ERG via the clarification process) indicates that assessment of HRQoL 'is provided as a separate report in appendix 16.1.13'. The company did not provide this appendix at the time of submission or during the clarification process.

In addition to the pre-planned ITT population, three additional subgroups were defined post-hoc and analysed within the CS: HDA-RRMS, RES-RRMS and SOT-RRMS subgroups (see Section 3.3 of this ERG report for further details of the subgroups). The ERG acknowledges that the post-hoc definition of subgroups, not originally included in the CLARITY trial, was necessary to address two of the subpopulations described in the NICE decision problem, but emphasises the decreased statistical power within these smaller subgroups which must be taken into account when interpreting the results of the post-hoc analyses of the CLARITY trial.

Table 12 CLARITY trial analysis populations

Analysis	Population
Efficacy (pre-planned)	Primary and secondary efficacy outcomes which were pre-planned and were analysed in the ITT population which was defined as all participants who underwent randomisation
Efficacy (post-hoc)	Primary and secondary efficacy outcomes, including outcomes defined post-hoc and were analysed in the following populations: • ITT population which was defined as all participants who underwent randomisation • RES-RRMS subgroup defined as participants with ≥2 relapses in the prior year whether on treatment or not and participants with ≥1 T1Gd+ lesion • SOT-RRMS subgroup defined as participants with ≥1 relapse in the previous year while on treatment and participants with ≥1 T1 Gd+ lesion or ≥9 T2 lesions • HDA-RRMS subgroup defined as participants with one relapse in the previous year while on disease modifying therapy and ≥1 T1 Gd+ lesion or ≥9 T2 lesions or participants with ≥2 relapses in the prior year whether on treatment or not
Safety (pre-planned)	The safety population was defined as all participants who received at least one dose of a study drug and for whom follow-up safety data were available

Gd+=gadolinium enhancing; HDA=high disease activity; ITT=intention-to-treat; RES=rapidly evolving severe; RRMS=relapsing-remitting multiple sclerosis; SOT=sub-optimal therapy;
Source: CS, Table 28, CLARITY TSAP (p85)

Outcomes and analysis approach in the CLARITY trial

The primary objective of the CLARITY trial was to evaluate the efficacy of cladribine tablets versus placebo in the reduction of qualifying ARR during 96 weeks of treatment in participants with RRMS.

Definitions and methods of statistical analysis for the primary efficacy outcome and important secondary efficacy outcomes of the CLARITY trial used within the economic model or relevant to the final NICE scope are provided in Table 13.

Table 13 Description and method of analysis for key efficacy outcomes in the CLARITY trial

Outcome	Outcome definition	Statistical analysis[a]
Primary efficacy outcome (pre-planned)		
Qualifying ARR	Qualifying annualised relapse rate at 96 weeks A relapse was defined as a two grade increase in ≥1 KFS or a one grade increase in ≥2 KFS, excluding changes in bowel/bladder or cognition, in the absence of fever, lasting for ≥24 hours, and preceded by ≥30 days of clinical stability or improvement	The ARR endpoint was analysed using a Poisson regression model with a fixed-effect for treatment group with log of time on trial as an offset variable The ratio of qualifying annualised relapsed rates in each of the cladribine groups vs the placebo group and the associated 95% (or 97.5% to account for multiple testing) confidence intervals (CI) were estimated An approximate Chi-square test based on Wald statistics was used to compare ARR in treatment groups and Hochberg's step-up method for multiple comparisons to protect the type I error

Other efficacy outcomes used in the economic model / specified in the scope (pre-planned)		
RF	Proportion of (qualifying) relapse-free participants at 96 weeks A relapse was defined as for primary outcome 'Qualifying ARR'	Analysed using a logistic-regression model with a fixed-effect for treatment group The odds ratio of being (qualifying) relapse-free in each of the cladribine groups vs the placebo group and the associated 95% (or 97.5% to account for multiple testing, see 'Qualifying ARR') confidence intervals (CI) were estimated
3 month CDP	Time to 3-month CDP at 96 weeks CDP is defined as a sustained change in EDSS ≥1 point, or ≥1.5 points if baseline EDSS was 0	Analysed with the use of a Cox proportional-hazards model with a fixed-effect for treatment group The time to 3-month CDP was measured as: date associated with the first 3-month CDP – start date of treatment + 1 Subjects that discontinued before week 96 without 3-month CDP, as well as subjects without 3-month CDP were censored and their time on study was used in the time to event analysis The hazard ratio of time to 3-month CDP at 96 weeks in each of the cladribine groups vs the placebo group and the associated 95% (or 97.5% to account for multiple testing, see 'Qualifying ARR) confidence intervals (CI) were estimated Kaplan-Meier plots by treatment group were also generated
	Proportion of participants with 3-month CDP at 48 weeks and at 96 weeks CDP is defined as a sustained change in EDSS ≥1 point, or ≥1.5 points if baseline EDSS was 0	Analysed using equivalent methodology as 'Proportion of (qualifying) relapse-free participants at 96 weeks'
Time to first qualifying relapse	Time to first qualifying relapse A relapse was defined as for primary outcome 'Qualifying ARR'	Analysed using equivalent methodology as 'Time to 3-month CDP at 96 weeks'

Other efficacy outcomes used in the economic model / specified in the scope (post-hoc)		
NEDA-3	NEDA-3 was defined as the absence of disease activity (all three conditions must be met): • No relapse at 96 weeks • No 3-month CDP • No new T1 Gd+ or active T2 lesions Complete definitions of each condition are provided in the company response to the ERG clarification letter	The primary measurement for assessment of absence of disease activity (NEDA-3) was be the Kaplan-Meier estimated cumulative probability of the disease-free state by 48 and 96 weeks for the CLARITY trial The outcome was also analysed with the use of a Cox proportional hazards model where time to disease activity (days) was calculated as the: date of first occurrence of disease activity – randomisation date + 1 Participants were censored if there was a disease event, defined as any of the following • Qualifying relapse • 3 month CDP • new or enhancing Gd+ T1 lesion • new or enlarging T2 lesion Or if absence of disease activity was unknown Participants were censored on their last date in the study or at the date of their last complete MRI assessment if their status was unknown All analyses were stratified by treatment naïve and previously treated participants Further definitions of the assessments at 48 weeks and 96 weeks are provided in the company response to the ERG clarification letter
6 month CDP	Time to 6-month CDP at 96 weeks CDP is defined as a sustained change in EDSS ≥1 point, or ≥1.5 points if baseline EDSS was 0	Analysed using equivalent methodology as 'Time to 3-month CDP at 96 weeks'
	Proportion of participants with 6-month CDP at 48 weeks and at 96 weeks CDP is defined as a sustained change in EDSS ≥1 point, or ≥1.5 points if baseline EDSS was 0	Analysed using equivalent methodology as 'Proportion of (qualifying) relapse-free participants at 96 weeks' Further definitions of the assessments at 48 weeks and 96 weeks are provided in the company response to the ERG clarification letter

ARR=annualised relapse rate; CDP=confirmed disability progression; EDSS=expanded disability status scale; Gd+=gadolinium-enhancing; KFS=kurtzke functional systems; NEDA-3=absence of disease activity; RF=relapse-free
Source: CS, Section B.2.3.3; TSAP (p94-96)

The ERG is satisfied that, for the pre-planned outcomes, the outcome definition and the analysis method for each of the efficacy outcomes were pre-specified in the TSAP, and that all results are reported fully in the CSR. The company notes that the original pre-planned analyses were conducted with region as a fixed-effect within statistical models, however, this fixed-effect was omitted from the re-analyses conducted for the CS, due to concerns regarding statistical model convergence within the smaller post-hoc subgroups. The definition of a relapse during the trial was pre-defined in the TSAP (p9) and an independent evaluating physician who was unaware of treatment allocations within the trial performed neurologic

examinations and determined whether a clinical event fulfilled criteria consistent with a relapse.[27]

The ERG notes that several terms are used interchangeably in the CS and related documents (TSAP, protocol, CLARITY trial publication, CSR) referring to endpoints related to disability; such as confirmed disease progression, confirmed disability progression, sustained progression of disability and sustained change in EDSS score. For consistency of terminology, this ERG report uses the term CDP to refer to endpoints related to disability as this terminology is closest to the outcomes specified in the NICE scope. The definition of CDP used within the CLARITY trial was pre-defined in the TSAP (p95).

Comparison of the three treatment groups of the CLARITY trial (3.5 mg/kg cladribine tablets, 5.25 mg/kg cladribine tablets and placebo) for all pre-planned primary and secondary efficacy outcomes was performed via an approximate Chi-square test based on Wald Statistics and Hochberg's step-up method for multiple comparisons to protect the type I error. Treatment effect estimates with 95% confidence intervals (CI) were presented if cladribine doses were significantly different from placebo, and 97.5% CIs were to be presented if only one cladribine dose was significantly different from placebo.

Three outcomes were defined by the company post-hoc and presented in the CS: NEDA-3, time to 6-month CDP and proportion of participants with 6-month CDP. The company states that NEDA-3 was captured post-hoc for the CLARITY trial due to the publication of literature after the completion of the CLARITY trial in 2010 suggesting that that freedom from disease activity was becoming an increasingly important endpoint in MS and that this outcome could be used to measure treatment effect beyond the duration of a trial.[39-41] Since the completion of the CLARITY trial, the EMA has released guidance[42] recommending the use of 6-month CDP to define sustained accumulation of disability, in line with this, the company has also reported time to 6-month CDP and proportion of participants with 6-month CDP post-hoc for the CLARITY trial in the CS. Clinical advice to the ERG is that NEDA-3 and CDP scores have not been validated as predictors of long-term outcome.

The ERG notes that the Cox regression methodology employed for the analysis of pre-planned outcomes (i.e., time to 3-month CDP and time to first qualifying relapse) and post-hoc outcomes (i.e., time to 6-month CDP and time to achieve NEDA-3 status) require the assumption of proportional hazards (PH) for the interpretation of estimated hazard ratios (HRs). The PH assumption was not originally tested for any of the pre-planned outcomes of the CLARITY trial or the post-hoc outcomes presented in the CS. In response to the ERG clarification letter, the company provided plots of the log (-log [Estimated Survival Distribution

Function]) against log (Time since Study Entry) for each outcome analysed by Cox regression methodology for the ITT population and for each of the three post-hoc subgroups. The company concludes that the lines on the plots are close to parallel in the entire ITT population and within the subgroups and therefore the PH assumption holds. The ERG agrees with this assessment for the ITT population and the HDA-RRMS subgroup, but considers the plots for the RES-RRMS and SOT-RRMS subgroups for each outcome difficult to interpret, due to the small numbers of participants within these subgroups.

Additional efficacy endpoints were also used for the CLARITY trial such as the endpoint associated with MRI lesions, severity of relapses, worsening of disease and rescue therapy use. These additional endpoints did not contribute to the economic model so are not discussed further within this ERG report. Further information regarding these outcomes is available in Section B.2.3.3 of the CS and numerical results for severity of relapses and worsening of disease were provided in the company response to the ERG clarification letter.

Patient reported endpoints (i.e. HRQoL) and safety endpoints (i.e. AEs) were also measured in the CLARITY and CLARITY-EXT trials. Further details of these outcomes are described in Section 4.4 and Section 4.5 of this ERG report respectively.

ERG assessment of the statistical approach of the CLARITY trial

A summary of the additional checks made by the ERG in relation to the pre-planned statistical approach used by the company to analyse data from the CLARITY trials is provided in Table 14. Having carried out these checks, the ERG is satisfied with the pre-planned statistical approach employed by the company but notes that information regarding the pre-planned methodology relating to HRQoL is limited.

The ERG acknowledges that three subgroups (Table 12) and three outcomes (Table 13) were defined post-hoc following the completion of the CLARITY trial. From the information provided in the CS and additional information provided by the company in response to the ERG clarification letter, the ERG is satisfied that the statistical approach of the post-hoc analyses employed by the company was appropriate. The ERG notes the inherent limitation of reduced statistical power when conducting post-hoc analyses, particularly within smaller subgroups than originally defined, as is the case within the CLARITY trial.

Table 14 ERG assessment of statistical approach used to analyse data from the CLARITY trials

Component	Statistical approach with ERG comments
Sample size calculation	The sample size calculation is presented in Table 16 of the CS: A sample size of 1290 participants (430 participants in each treatment arm) provided 90% power to detect a clinically meaningful 25% relative reduction in ARR at 96 weeks when comparing each of the cladribine tablets arms to the placebo arm. The target sample was calculated using a 2-sided t-test assuming 1) the mean number of qualifying relapses during 96 weeks was 2.1 for the placebo treatment arm, 2) a relative 25% reduction in mean number of qualifying relapses and 3) a common standard deviation of 2.02 for the number of qualifying relapses, a 10% non-evaluable rate and a type I error rate for each cladribine tablets group versus the placebo group at 2.5%. Assumptions regarding the number of relapses were based on 2-year data from the placebo group of the PRISMS trial.[43] The ERG is satisfied that this sample size calculation was provided in the TSAP (p84).
Protocol amendments	Protocol amendments were provided by the company, in addition to an original protocol and the final protocol with all amendments incorporated. Nine amendments were made between March 2005 and September 2008. All amendments and rationale for amendments are outlined in detail. Four amendments were made to adapt the trial procedures to country specific regulations and five amendments were made to trial procedures such as eligibility criteria, baseline assessment, definitions and measurement times of endpoints, adverse event recording, trial visit times and statistical analysis methodology. The ERG is satisfied with the rationale for the amendments and that all amendments were made before the trial completion date (date of last subject last visit was 12 November 2008, CSR, p1) and before the post-hoc analyses undertaken within the CS so amendments were unlikely to have been driven by the results of the trial.
Imputation of missing data	The approach to handling missing data for the re-analysis of the CLARITY trial presented within the CS was amended to an approach the company considers more appropriate to the original approach specified within the TSAP (outlined on p130-133 for efficacy outcomes and MRI outcomes). Details of the differences in the analysis approaches to missing data are outlined in Appendix 11.1 of this ERG report. The principal differences between the approaches were that data were not excluded or imputed for participants receiving rescue medication and, rather than imputing event times, participants with missing data were considered as 'unknown' in time-to-event analyses. The ERG agrees with the company that the approach in the re-analysis was more appropriate than the approach in the original analysis.

Component	Statistical approach with ERG comments
Pre-planned subgroup analyses	Pre-planned subgroup analyses of key efficacy endpoints in the CLARITY trial are available in the TSAP (p138). If a statistically significant and clinically relevant treatment by region interaction was found, summaries of treatment by region were performed. If at least 10% of the subjects received any disease modifying drug as rescue medication, a parameter for intake the rescue medication and an interaction term between treatment and intake of rescue medication would be added into the models for the continuous efficacy parameters. If the interaction is significant and clinically relevant, separate analyses would have been will be conducted for those who took combination therapy and those who did not take any rescue medication. The ERG is satisfied that results of pre-planned subgroup analyses by region are presented within the CSR (p357-365) for all efficacy outcomes. The ERG notes that these subgroup analyses were not presented in the CS. The ERG is satisfied that no subgroup analysis of rescue medication was performed, as only 3.5% of participants received rescue medication (CSR, p167). The ERG notes that subgroup analyses presented within the CS were defined post-hoc so were not included in the CLARITY protocol, TSAP or CSR.
Pre-planned sensitivity analyses	Pre-planned sensitivity analyses of key efficacy endpoints in the CLARITY trial are available in the TSAP (p138-139). Sensitivity analyses to examine the robustness of results were planned with modified treatment groups to take account of combination therapy if at least 10% of the subjects received any disease modifying drug as rescue medication. Sensitivity analysis was also planned to take account of any baseline imbalance, defined as a statistically significant difference between the treatment groups in any baseline parameter. The ERG assumes that these sensitivity analyses were not carried out as less than 10% of subjects received rescue medication (CSR, p167) and as there were no statistically significant imbalances in any baseline parameter (CSR, p95), although this is not explicitly stated within the CSR.
Analysis of AEs	Many different summaries of AEs are provided in the CSR. All AEs, TEAEs, SAEs, deaths, AEs leading to treatment and study discontinuation are summarised by treatment group, by study time period (Week 0 to 48, Week 48 to 96), by region and by system organ class. Pre-specified TEAEs are presented separately. Numbers of events and number of events per subject, in addition to the incidence rates of events (number of occurrences of a specific event divided by the total number of all events) are presented. The ERG is satisfied that the methodology used to analyse the AEs is appropriate and was pre-specified in the TSAP (p106-114) and that all summary tables of AEs are presented within the CSR (p445-1045).

Component	Statistical approach with ERG comments
Analysis of PROs	HRQoL was assessed by the change from baseline to 96 weeks in MSQOL-54 (physical function, role limitations-physical, role limitations-emotional, health perceptions, mental health and change in health) and the SF-36 Health Survey (physical functioning, role, general health and mental health). Additional subscales of the HRQoL tools were also considered. Treatment effect comparisons were based on the change from baseline to 96 weeks in the mean score of the respective scales using an two-way ANOVA model with effects for treatment, region and their interaction (included if significant or removed if non-significant). A p-value of <=0.05 in the treatment effect will be considered statistically significant. Where applicable, last observation carried forward (LOCF) method would be used to substitute for missing post-baseline data. The ERG notes that the statistical methodology for analysing HRQoL is presented in the protocol (p69-70) but is not presented in the TSAP. The ERG is mostly satisfied that the methodology used to analyses HRQoL was appropriate but is concerned about the use of LOCF method for imputing missing post-baseline data due to the biases associated with this method.[44] The ERG acknowledges that imputed and non-imputed results are provided in the CS (p44) and there are no changes in conclusions.

AE=adverse event; AESI=adverse events of special interest; ANOVA=analysis of variance; CI=confidence interval; CS=company submission; CSR=clinical trial report; ERG=Evidence Review Group; HRQoL=health-related quality of life; K-M=Kaplan-Meier; LOCF=last observation carried forward; MRI=magnetic resonance imaging; MSQOL-54=multiple sclerosis quality of life-54; PRO=patient-reported outcome; SAE=serious adverse events SD=standard deviation; SF-36=36 item short form; TEAE=treatment emergent adverse event; TSAP=trial statistical analysis plan
Source: adapted from the CS, CLARITY CSR, CLARITY protocol, CLARITY TSAP, the company's response to the ERG clarification letter, and ERG comment

4.2.5 Risk of bias assessment for the CLARITY trial

The company assessed the risk of bias in the CLARITY trial using the minimum criteria set out in the NICE Guide to the Methods of Technology appraisal.[31] The company's risk of bias assessment, and ERG comments, are presented in Table 15.

The ERG considers that the risk of bias in the CLARITY trial was low for four of the seven criteria, and unclear for the remaining criteria. The ERG agrees with the company that there was a lower proportion (≈5%) of patients who had received previous therapy with any DMT in the cladribine 3.5 mg/kg group than in the placebo or cladribine 5.25 mg/kg groups. Disease duration from time of onset was statistically significantly lower in the cladribine tablets 3.5 mg/kg group (7.9±7.2 years) than in the placebo (8.9±7.4 years) or cladribine tablets 5.25 mg/kg (9.3±7.6 years) groups. Although the trial is described as being double-blinded, the treating physician was not blinded to treatment allocation. The company states that the methods used to account for missing data in the post-hoc analyses presented in the CS were more appropriate than the methods used for this purpose in the CSR. The ERG agrees with this conclusion (further discussed in Section 4.2.4).

Table 15 Risk of bias assessment of the CLARITY trial

Study question	Company assessment		ERG comment
	Addressed in the trial	Risk of bias	
Was randomisation carried out appropriately?	Yes	Low	Agree - computer-generated randomisation schedule
Was the concealment of treatment allocation adequate?	Yes	Low	Agree - treatment allocation concealed from evaluating physician
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Low	Unclear - differences in previous treatment with DMTs and disease duration from time of onset
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Low	Unclear - treating physician and study coordinators were aware of treatment allocation. Participants and physicians performing neurologic examinations were blinded to treatment allocation
Were there any unexpected imbalances in drop-outs between groups?	No	Low	Agree - similar proportions of drop-outs across the three groups
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Low	Unclear - SF-36 data were collected but the company was unable to analyse the results due to a lack of availability of baseline measures
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. Appropriate methods were used to account for missing data	Low	Agree - analyses were performed according to the ITT principle and appropriate methods used to account for missing data

DMT=disease-modifying therapy; ITT=intention-to-treat; SF-36=36-Item Short Form Survey
Source: CS, Table 17, document embedded to Appendix D

4.3 Results from the CLARITY trial

All results from the CLARITY trial presented in this section come from post-hoc analyses which were performed between 18th July 2016 and 10th August 2016.[26]

There are minor discrepancies between the results presented within the CS (and within this ERG report) and the results presented within the CSR for the CLARITY trial and the primary publication,[27] which were both prepared in 2010. Detailed reasons for the differences in the numerical results due to the differences in statistical modelling are presented in Appendix 10.1 of this ERG report.

4.3.1 Participant flow in the CLARITY trial

A total of 1326 participants were randomised in the CLARITY trial; 437 to the placebo treatment arm, 433 to the 3.5 mg/kg cladribine tablets treatment arm and 456 to the 5.25 mg/kg cladribine tablets treatment arm.

Table 16 summarises the participant flow in the cladribine tablets and placebo treatment arms; 398 (91.9%) participants in the cladribine tablets arm completed the 96-week study (of which 395 [91.2%] completed treatment) and 380 (87.0%) participants in the placebo arm completed the 96-week study (of which 377 [86.3] completed treatment).

The mean time of participation in the CLARITY trial was 91.0 weeks in the cladribine tablets arm and 87.8 weeks in the placebo arm.[27]

Table 16 Participant disposition in the CLARITY trial

Number of participants	Cladribine tablets	Placebo
Randomised	433	437
Completed 96 week study: n (% of randomised)	398 (91.9)	380 (87.0)
Completed Treatment: n (% of randomised)	395 (91.2)	377 (86.3)
Withdrew: n (% of randomised)	35 (8.1)	57 (13.0)
• Lost to follow-up	• 8 (1.8)	• 4 (0.9)
• Adverse event	• 5 (1.2)	• 5 (1.1)
• Protocol violation	• 4 (0.9)	• 10 (2.3)
• Insufficient efficacy	• 5 (1.2)	• 21 (4.8)
• Death	• 1 (0.2)	• 2 (0.5)
• Other[a]	• 12 (2.6)	• 15 (3.4)

[a] Other reasons for discontinuation were consent withdrawal for administrative, convenience and personal reasons.
Source: CS, adapted from Appendix D 1.2.1; Giovannini et al 2010, adapted from Supplemental Figure 2

As introduced in earlier sections of this ERG report, in addition to the ITT population (i.e. all randomised participants), three post-hoc subgroups were defined for analysis; HDA-RRMS, RES-RRMS and SOT-RRMS. The number of participants within each of the analysis subgroups from the CLARITY trial is presented in Table 11.

4.3.2 Primary efficacy outcome: qualifying annualised relapse rate

The primary efficacy outcome of the CLARITY trial was qualifying ARR, measured at 96 weeks; results for the ITT population of the CLARITY trials and the three post-hoc subgroups are presented in Table 17.

Cladribine tablets were associated with a statistically significant relative reduction in qualifying ARR compared with placebo within the ITT population, HDA-RRMS subgroup and RES-RRMS-subgroup. There was also a numerical advantage for cladribine tablets over placebo in the SOT-RRMS subgroup, but this reduction was not statistically significant. The ERG notes that due to the small numbers of participants within the SOT-RRMS subgroup (19 and 32 for cladribine tablets and placebo respectively), it is unlikely that this post-hoc analysis, or any of the post-hoc analyses within this subgroup, has the statistical power to detect a difference between the treatments.

Table 17 Qualifying ARR results at 96 weeks in the CLARITY trial (ITT population and post-hoc subgroups)

Outcome	Cladribine tablets	Placebo
ITT population		
Number of participants analysed	433	437
Qualifying ARR (95% CI)	0.14 (0.12 to 0.17)	0.34 (0.30 to 0.38)
Relative reduction in ARR (%)	58.22	
Rate ratio (95% CI, p-value)	0.42 (0.33 to 0.53; p<0.001)	
HDA-RRMS subgroup		
Number of participants analysed	140	149
Qualifying ARR (95% CI)	0.16 (0.12 to 0.22)	0.46 (0.38 to 0.55)
Relative reduction in ARR (%)	65.29	
Rate ratio (95% CI, p-value)	0.35 (0.24 to 0.50; p<0.0001)	
RES-RRMS subgroup		
Number of participants analysed		
Qualifying ARR (95% CI)		
Relative reduction in ARR (%)		
Rate ratio (95% CI, p-value)		
SOT-RRMS subgroup		
Number of participants analysed		
Qualifying ARR (95% CI)		
Relative reduction in ARR (%)		
Rate ratio (95% CI, p-value)		

ARR=annualised relapse rate; CI=confidence interval, HDA=high disease activity; ITT=intention-to-treat; RES=rapidly evolving severe; RRMS=relapsing-remitting multiple sclerosis; SOT=sub-optimal therapy
Source: CS, adapted from Table 18 and Table 30

4.3.3 Secondary efficacy outcomes: pre-planned outcomes

A pre-planned secondary outcome of the CLARITY trial was time to first qualifying relapse; results for the ITT population of the CLARITY trial and the three post-hoc subgroups are presented in Table 18.

Cladribine tablets were associated with a statistically significant delay in time to first qualifying relapse compared with placebo within the ITT population, HDA-RRMS subgroup and RES-RRMS-subgroup. There was also a numerical advantage for cladribine tablets over placebo in the SOT-RRMS subgroup, but this delay was not statistically significant.

Table 18 Time to first qualifying relapse in the CLARITY trial (ITT population and post-hoc subgroups)

Outcome	Cladribine tablets	Placebo
ITT population		
Number of participants analysed	433	437
K-M estimate of relapse-free participants, % (95% CI)	80.3 (76.1 to 83.8)	61.1 (56.2 to 65.6)
HR (95% CI, p-value)	0.45 (0.34 to 0.58; p<0.0001)	
HDA-RRMS subgroup		
Number of participants analysed	140	149
K-M estimate of relapse-free participants, % (95% CI)	77.1 (68.8 to 83.5)	53.3 (44.7 to 61.2)
HR (95% CI, p-value)	0.40 (0.26 to 0.61; p<0.0001)	
RES-RRMS subgroup		
Number of participants analysed	[redacted]	[redacted]
K-M estimate of relapse-free participants, % (95% CI)	[redacted]	[redacted]
HR (95% CI, p-value)	[redacted]	
SOT-RRMS subgroup		
Number of participants analysed	[redacted]	[redacted]
K-M estimate of relapse-free participants, % (95% CI)	[redacted]	[redacted]
HR (95% CI, p-value)	[redacted]	

CI=confidence interval; HDA=high disease activity; HR=hazard ratio; ITT=intention-to-treat; K-M=Kaplan-Meier; RES=rapidly evolving severe; RRMS=relapsing-remitting multiple sclerosis; SOT=sub-optimal therapy
Source: CS, adapted from Table 18 and Table 31

Another pre-planned secondary outcome of the CLARITY trial was the proportion of qualifying relapse-free participants at 48 weeks and at 96 weeks; results for the ITT population of the CLARITY trials and the three post-hoc subgroups are presented in Table 19. A higher proportion of participants were qualifying relapse-free at 48 weeks and 96 weeks in the cladribine tablets group compared to the placebo group in the ITT population and in the three post-hoc subgroups.

Table 19 Proportion of qualifying relapse-free participants in the CLARITY trial (ITT population and post-hoc subgroups)

Outcome	Cladribine tablets		Placebo	
Measurement time	**48 weeks**	**96 weeks**	**48 weeks**	**96 weeks**
ITT population				
Number of participants analysed	433	433	437	437
Relapse, n (%)	60 (13.9)	82 (18.9)	110 (25.2)	161 (36.8)
Relapse-free, n (%)	353 (81.5)	327 (75.5)	300 (68.6)	237 (54.2)
Unknown,[a] n (%)	20 (4.6)	24 (5.5)	27 (6.2)	39 (8.9)
HDA-RRMS subgroup				
Number of participants analysed	140	140	149	149
Relapse, n (%)	21 (15.0)	30 (21.4)	50 (33.6)	66 (44.3)
Relapse-free, n (%)	112 (80.0)	101 (72.1)	89 (59.7)	69 (46.3)
Unknown,[a] n (%)	7 (5.0)	9 (6.4)	10 (6.7)	14 (9.4)
RES-RRMS subgroup				
Number of participants analysed	[redacted]	[redacted]	[redacted]	[redacted]
Relapse, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Relapse-free, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Unknown,[a] n (%)	[redacted]	[redacted]	[redacted]	[redacted]
SOT-RRMS subgroup				
Number of participants analysed	[redacted]	[redacted]	[redacted]	[redacted]
Relapse, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Relapse-free, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Unknown,[a] n (%)	[redacted]	[redacted]	[redacted]	[redacted]

[a] Participants who withdrew early before week 48/96 with no relapse are categorised as unknown (For week 96, 'early' was considered to be <83 weeks)
CDP=confirmed disability progression; HDA=high disease activity; HR=hazard ratio; ITT=intention-to-treat; RES=rapidly evolving severe; RRMS=relapsing-remitting multiple sclerosis; SOT=sub-optimal therapy
Source: CS, adapted from Table 19 and Table 32; CLARITY GEVD subgroup analyses (Merck. (2017c), data on file)

Two secondary outcomes associated with disability were pre-planned in the CLARITY trial. Results of time to 3-month CDP for the ITT population of the CLARITY trial and the three post-hoc subgroups are presented in Table 20.

Cladribine tablets were associated with a statistically significant delay in time to 3-month CDP compared with placebo within the ITT population and HDA-RRMS subgroup. There was also a numerical advantage for cladribine tablets over placebo in the RES-RRMS-subgroup, but this delay was not statistically significant. The comparative risk of disability progression at 96 weeks in the treatment groups could not be evaluated in the SOT-RRMS subgroup as no participants in the cladribine tablets group had confirmed 3-month CDP at 96 weeks within this subgroup (Table 20).

Table 20 Time to 3-month CDP in the CLARITY trial (ITT population and post-hoc subgroups)

Outcome	Cladribine tablets	Placebo
ITT population		
Number of participants analysed	433	437
K-M estimate of progression-free participants, % (95% CI)	85.1 (81.3 to 88.2)	76.3 (71.9 to 80.2)
HR (95% CI, p-value)	0.59 (0.43 to 0.81; p=0.0011)	
HDA-RRMS subgroup		
Number of participants analysed	140	149
K-M estimate of progression-free participants, % (95% CI)	91.0 (84.7 to 94.8)	71.7 (63.4 to 78.5)
HR (95% CI, p-value)	0.28 (0.15 to 0.54; p=0.0001)	
RES-RRMS subgroup		
Number of participants analysed		
K-M estimate of progression-free participants, % (95% CI)		
HR (95% CI, p-value)		
SOT-RRMS subgroup		
Number of participants analysed		
K-M estimate of progression-free participants, % (95% CI)		
HR (95% CI, p-value)		

CI=confidence interval; HDA=high disease activity; HR=hazard ratio; ITT=intention-to-treat; K-M=Kaplan-Meier; NE=not estimable; RES=rapidly evolving severe; RRMS=relapsing-remitting multiple sclerosis; SOT=sub-optimal therapy
Source; CS, adapted from Table 20 and Table 33

Results of the proportion of participants with 3-month CDP for the ITT population of the CLARITY trial and the three post-hoc subgroups are presented in Table 21. A lower proportion of participants had 3-month CDP at 48 weeks and 96 weeks in the cladribine tablets group compared to the placebo group in the ITT population and in the three post-hoc subgroups.

Table 21 Proportion of participants with 3-month CDP in the CLARITY trial (ITT population and post-hoc subgroups)

Outcome	Cladribine tablets		Placebo	
Measurement time	**48 weeks**	**96 weeks**	**48 weeks**	**96 weeks**
ITT population				
Number of participants analysed	433	433	437	437
Progression, n (%)	36 (8.3)	62 (14.3)	65 (14.9)	97 (22.2)
Progression-free, n (%)	377 (87.1)	344 (79.4)	340 (77.8)	292 (66.8)
Unknown,[a] n (%)	20 (4.6)	27 (6.2)	32 (7.3)	48 (11.0)
HDA-RRMS subgroup				
Number of participants analysed	140	140	149	149
Progression, n (%)	6 (4.3)	12 (8.6)	27 (18.1)	39 (26.2)
Progression-free, n (%)	126 (90.0)	116 (82.9)	109 (73.2)	89 (59.7)
Unknown,[a] n (%)	8 (5.7)	12 (8.6)	13 (8.7)	21 (14.1)
RES-RRMS subgroup				
Number of participants analysed	[redacted]	[redacted]	[redacted]	[redacted]
Progression, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Unknown,[a] n (%)	[redacted]	[redacted]	[redacted]	[redacted]
SOT-RRMS subgroup				
Number of participants analysed	[redacted]	[redacted]	[redacted]	[redacted]
Progression, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Unknown,[a] n (%)	[redacted]	[redacted]	[redacted]	[redacted]

[a] Participants who withdrew early before week 48/96 with 3 month-CDP are categorised as unknown (For week 96, 'early' was considered to be <83 weeks)
CDP=confirmed disability progression; HDA=high disease activity; HR=hazard ratio; ITT=intention-to-treat; RES=rapidly evolving severe; RRMS=relapsing-remitting multiple sclerosis; SOT=sub-optimal therapy
Source: CS, adapted from Table 21 and Table 34; CLARITY GEVD subgroup analyses (Merck. (2017c), data on file)

As noted in Section 4.3.2 of the ERG report, the ERG re-iterates that due to the small numbers of participants within the SOT-RRMS subgroup (19 and 32 for 3.5 mg/kg cladribine tablets and placebo, respectively), it is unlikely that any of the post-hoc analyses of the secondary efficacy outcomes has the statistical power to detect a difference between the treatments.

4.3.4 Secondary efficacy outcomes: post-hoc analyses

Two additional secondary outcomes associated with disability were defined in a post-hoc analysis to demonstrate prolonged efficacy in the reduction of disability progression following 3.5 mg/kg cladribine tablets. Results of time to 6-month CDP for the ITT population of the CLARITY trial and the three post-hoc subgroups are presented in Table 22.

Cladribine tablets were associated with a statistically significant delay in time to 3-month CDP compared with placebo within the ITT population and HDA-RRMS subgroup. There was also a numerical advantage for cladribine tablets over placebo in the RES-RRMS-subgroup, but this delay was not statistically significant. The comparative risk of disability progression at 96

weeks in the treatment groups could not be evaluated in the SOT-RRMS subgroup as no participants in the cladribine tablets group had confirmed 3-month CDP at 96 weeks within this subgroup (Table 22).

Table 22 Time to 6-month CDP in the CLARITY trial (ITT population and post-hoc subgroups)

Outcome	Cladribine tablets	Placebo
ITT population		
Number of participants analysed	433	437
K-M estimate of progression-free participants, % (95% CI)	90.6 (87.4 to 93.1)	83.3 (79.3 to 86.6)
HR (95% CI, p-value)	0.53 (0.36 to 0.78; p=0.0014)	
HDA-RRMS subgroup		
Number of participants analysed	140	149
K-M estimate of progression-free participants, % (95% CI)	95.5 (90.2 to 97.9)	77.7 (69.8 to 83.8)
HR (95% CI, p-value)	0.18 (0.08 to 0.44; p=0.0001)	
RES-RRMS subgroup		
Number of participants analysed		
K-M estimate of progression-free participants, % (95% CI)		
HR (95% CI, p-value)		
SOT-RRMS subgroup		
Number of participants analysed		
K-M estimate of progression-free participants, % (95% CI)		
HR (95% CI, p-value)		

CDP=confirmed disability progression; CI=confidence interval; HDA=high disease activity; HR=hazard ratio; ITT=intention-to-treat; K-M=Kaplan-Meier; NE=not evaluable; RES=rapidly evolving severe; RRMS=relapsing-remitting multiple sclerosis; SOT=sub-optimal therapy
Source: CS, adapted from Table 22 and Table 35

Results of the proportion of participants with 6-month CDP for the ITT population of the CLARITY trial and the three post-hoc subgroups are presented in Table 23. A lower proportion of participants had 6-month CDP at 48 weeks and 96 weeks in the cladribine tablets group compared to the placebo group in the ITT population and in the three post-hoc subgroups.

Table 23 Proportion of participants with 6-month CDP in the CLARITY trial (ITT population and post-hoc subgroups)

Outcome	Cladribine tablets		Placebo	
Measurement time	**48 weeks**	**96 weeks**	**48 weeks**	**96 weeks**
ITT population				
Number of participants analysed	433	433	437	437
Progression, n (%)	25 (5.8)	39 (9.0)	53 (12.1)	69 (15.8)
Progression-free, n (%)	386 (89.1)	363 (83.8)	348 (79.6)	315 (72.1)
Unknown,[a] n (%)	22 (5.1)	31 (7.2)	36 (8.2)	53 (12.1)
HDA-RRMS subgroup				
Number of participants analysed	140	140	149	149
Progression, n (%)	2 (1.4)	6 (4.3)	23 (15.4)	31 (20.8)
Progression-free, n (%)	129 (92.1)	121 (86.4)	112 (75.2)	96 (64.4)
Unknown,[a] n (%)	9 (6.4)	13 (9.3)	14 (9.4)	22 (14.8)
RES-RRMS subgroup				
Number of participants analysed	[redacted]	[redacted]	[redacted]	[redacted]
Progression, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Unknown,[a] n (%)	[redacted]	[redacted]	[redacted]	[redacted]
SOT-RRMS subgroup				
Number of participants analysed	[redacted]	[redacted]	[redacted]	[redacted]
Progression, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Unknown,[a] n (%)	[redacted]	[redacted]	[redacted]	[redacted]

[a] Participants who withdrew early before week 48/96 with 6-month CDP are categorised as unknown (For week 96, 'early' was considered to be <83 weeks)
CDP=confirmed disability progression; HDA=high disease activity; HR=hazard ratio; ITT=intention-to-treat; RES=rapidly evolving severe; RRMS=relapsing-remitting multiple sclerosis; SOT=sub-optimal therapy
Source: CS, adapted from Table 22 and Table 36; CLARITY GEVD subgroup analyses (Merck. (2017c), data on file)

An additional post-hoc composite efficacy outcome, NEDA-3, was defined as no relapses, no 3-month confirmed EDSS progression, no new or enhancing T1 Gd+ lesions and no new or enlarging T2 lesions. Results of time to NEDA-3 for the ITT population of the CLARITY trial and the three post-hoc subgroups are presented in Table 24.

Cladribine tablets had no evidence of disease activity over the entire duration of the CLARITY trial compared to placebo within the ITT population and within all three post-hoc subgroups.

The ERG encourages caution when interpreting the results of these post-hoc analyses due to the inherent limitation of reduced statistical power, particularly within smaller subgroups than originally defined. In particular, the ERG notes caution when interpreting the result of 'time to achieve NEDA-3 status' in the SOT-RRMS subgroup; this is the only outcome for which a significant advantage to 3.5 mg/kg cladribine tablets over placebo is observed for this small subgroup.

Table 24 Time to achieve NEDA-3 status in the CLARITY trial (ITT population and post-hoc subgroups)

Outcome	Cladribine tablets	Placebo
ITT population		
Number of participants analysed	433	437
K-M estimate of NEDA-3 status, % of participants, (95% CI)	40.1 (34.5 to 45.6)	12.6 (8.8 to 17.0)
HR (95% CI, p-value)	2.21 (1.88 to 2.61, p<0.0001)	
HDA-RRMS subgroup		
Number of participants analysed	140	149
K-M estimate of NEDA-3 status, % of participants, (95% CI)	43.7 (35.0 to 52.0)	6.9 (2.8 to 13.6)
HR (95% CI, p value)	2.86 (2.14 to 3.81, p<0.0001)	
RES-RRMS subgroup		
Number of participants analysed	[redacted]	[redacted]
K-M estimate of NEDA-3 status, % of participants, (95% CI)	[redacted]	[redacted]
HR (95% CI, p value)	[redacted]	
SOT-RRMS subgroup		
Number of participants analysed	[redacted]	[redacted]
K-M estimate of NEDA-3 status, % of participants, (95% CI)	[redacted]	[redacted]
HR (95% CI, p value)	[redacted]	

CI=confidence interval; HDA=high disease activity; HR=hazard ratio; ITT=intention-to-treat; K-M=Kaplan-Meier; NEDA-3=no evidence of disease activity; RES=rapidly evolving severe; RRMS=relapsing-remitting multiple sclerosis; SOT=sub-optimal therapy
Source: CS, adapted from Table 23 and Table 37

4.4 Health-related quality of life

Three different questionnaires were used in the CLARITY trial to collect data on the impact of treatment with cladribine tablets on patients' HRQoL, namely:

- disease specific multiple sclerosis quality of life questionnaire (MSQoL-54)[45]
- EQ-5D-3L questionnaire and EQ visual analogue scale (VAS)[46]
- short-form health survey (SF-36)[47]

No statistically significant differences in any of the domains of the MSQoL-54 (CS, section B.2.6.1.4) were observed when treatment with cladribine tablets was compared with placebo. Statistically significant improvements in the EQ-5D VAS (p=0.001) and EQ-5D-3L index scores (p<0.001) were observed when treatment with cladribine tablets was compared to placebo.

In the CS, and in the CSR, it is mentioned that the MSQoL-54 and SF-36 questionnaires were not initiated at the start of the CLARITY trial and, therefore, a limited number of responses were obtained (CS, section B.2.6.1.4). The company claims (CSR, p50) that, as the MSQoL-54 questionnaire was not widely translated into non-English languages at the time when the

trial was conducted, the MSQoL-54 questionnaire was only applied to sites in the UK, US, Australia, Canada and Italy.

Analyses of HRQoL data to compare the effect of treatment with cladribine tablets versus the comparators included in the final scope issued by NICE are only presented for the ITT population, i.e. for the RRMS population (CS, Section B.2.6.1.4). Utility values obtained from the CLARITY trial for the RES-RRMS and SOT-RRMS subgroups based on the EQ-5D-3L questionnaire are provided in the CS (appendix H.1.4, pp107-108). Comparisons of cladribine tablets versus placebo using data only from the RES-RRMS and SOT-RRMS subgroups are not presented in the CS.

Given the limited information provided by the company in the CS, the ERG is unable to comment further on the HRQoL data from the CLARITY trial. Information in the CSR for the CLARITY trial (requested by the ERG via the clarification process) indicates that assessment of HRQoL 'is provided as a separate report in appendix 16.1.13'. The company did not provide this appendix at the time of submission or during the clarification process.

4.5 Adverse events

The AEs experienced by patients during the CLARITY trial are reported in the CS (Section B.2.10.1). The company has also provided supportive evidence for the safety of cladribine tablets from the CLARITY-EXT trial (CS, Section B.2.10.2) as well as results from an integrated safety analysis that includes data from four sources: the CLARITY trial, the CLARITY-EXT trial, the ORACLE MS trial[34] and the PREMIERE prospective registry study[33] (CS, Section B2.10.3). In this report, the ERG discusses only the AE data from the CLARITY trial as these are the data used to populate the company's economic model.

4.5.1 Adverse events reported in the CLARITY trial

The AEs reported in the CS are derived from the overall population of patients in the CLARITY trial who were randomised to receive cladribine tablets at a dose of 3.5 mg/kg (n=430) or placebo (n=435) and who received at least one study treatment. No AE data are provided for the RES-RRMS (n=91) and SOT-RRMS (n=51) subgroups of patients from the CLARITY trial. Clinical advice to the ERG is that the AEs recorded for the overall population of the CLARITY trial are relevant to the patients in the RES-RRMS and the SOT-RRMS subgroups.

Number of treatment cycles and treatment compliance

The ERG notes from the CSR for the CLARITY trial that [redacted] of patients treated with cladribine tablets completed all six cycles of treatment compared with [redacted] of patients in the placebo arm. The ERG also notes that treatment compliance was high at [redacted] and [redacted] in

the cladribine and placebo arms. The company measured treatment compliance as the number of tablets taken divided by the expected number of tablets that would be required by the protocol's defined body weight categories.

Treatment discontinuation due to AEs

The company reports that the proportions of patients who discontinued treatment due to AEs was low; 3.5% (n=15) of patients in the cladribine tablets arm and 2.1% (n=9) of patients in the placebo arm. The company provides a summary of the AEs that led to treatment discontinuation in Table 44 of the CS. The AEs in the cladribine arm included: lymphopenia, decreased lymphocyte count, abnormal lymphocyte count, toxic hepatitis, fibroadenoma of the breast, ovarian cancer, uterine leiomyoma, dermatitis, allergic dermatitis, erythematous rash, myocardial infarction, ulcerative colitis, nausea and breast mass. The AEs leading to treatment discontinuation in the placebo arm included: appendicitis, varicella, pregnancy, liver disorder, suicide, intentional self-injury, cough, pulmonary oedema, cardiac hypertrophy, anorexia, haemorrhagic stroke and nephrosclerosis. In most cases, AEs leading to treatment discontinuation were experienced by a single patient.

Treatment emergent adverse events

Overall treatment emergent adverse events

The company reports that the proportions of treatment-emergent AEs (TEAEs) were similar in the cladribine tablets arm and the placebo arm of the CLARITY trial (80.7% and 73.3%). The company has summarised the TEAEs reported in ≥5% of patients.

The ERG notes that most of the TEAEs listed in Table 25 were reported by more patients in the cladribine tablets arm compared to patients in the placebo arm; however, the differences in frequency were generally small. Larger differences in frequency are apparent between patients in the cladribine tablets arm compared to patients in the placebo arm for leukopenia (5.6% versus 0.7%) and lymphopenia (21.6% versus 1.8%). The company has discussed the relationship between lymphopenia and cladribine tablets in the TEAEs of special interest section of the CS. The company also states that the higher rate of leukopenia is linked to the higher rate of lymphopenia (CS, Section B.2.10.3.1).

The ERG notes that three TEAEs occurred in more patients in the placebo arm than in the cladribine tablets arm: urinary tract infection (9% versus 5.3%), fatigue (6% versus 4.7%) and pharyngolaryngeal pain (5.7% versus 4.4%).

Table 25 Summary of TEAEs reported in ≥5% of patients in the CLARITY trial

Adverse event	Cladribine tablets (3.5mg/kg) n=430		Placebo n=435	
	Patients (%)	Events (%)	Patients (%)	Events (%)
Headache	104 (24.2)	264 (10.5)	75 (17.2)	189 (9.7)
Lymphopenia	93 (21.6)	123 (4.9)	8 (1.8)	11 (0.6)
Nasopharyngitis	62 (14.4)	107 (4.3)	56 (12.9)	95 (4.9)
Upper respiratory tract infection	54 (12.6)	118 (4.7)	42 (9.7)	80 (4.1)
Nausea	43 (10.0)	74 (2.9)	39 (9.0)	49 (2.5)
Back pain	34 (7.9)	39 (1.6)	28 (6.4)	42 (2.1)
Urinary tract infection	23 (5.3)	39 (1.6)	39 (9.0)	51 (2.6)
Influenza-like illness	34 (7.9)	48 (1.9)	31 (7.1)	40 (2.0)
Diarrhoea	30 (7.0)	45 (1.8)	29 (6.7)	37 (1.9)
Influenza	28 (6.5)	34 (1.4)	27 (6.2)	43 (2.2)
Fatigue	20 (4.7)	27 (1.1)	26 (6.0)	29 (1.5)
Arthralgia	27 (6.30)	44 (1.8)	21 (4.8)	23 (1.2)
Pharyngolaryngeal pain	19 (4.4)	32 (1.3)	25 (5.7)	29 (1.5)
Leukopenia	24 (5.6)	26 (1.0)	3 (0.7)	6 (0.3)

TEAE=treatment emergent adverse event
Source: CS Table 45

Serious treatment emergent adverse events

The company reports that more patients in the cladribine tablets arm experienced serious TEAEs than in the placebo arm (8.4% versus 6.4%). The company summarises the serious TEAEs by category of system organ class and states that the system organ classes with the largest proportion of serious TEAEs are those listed in rows 1 to 3 of Table 26. The ERG has added the data in row 4 onwards (CSR, pp1002-3).

Table 26 Serious TEAEs in the CLARITY trial (largest proportions)

System organ class	Cladribine tablets (3.5mg/kg) n=430	Placebo n=435
Infections and infestations	2.3%	1.6%
Hepatobiliary disorders	0.7%	0.7%
Gastrointestinal disorders	0.9%	0.5%
Injury, poisoning and procedural complications	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]
Cardiac disorders	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]

Source: CS Section B.2.10.1.2 and CLARITY CSR (p1002 and 1003)

Two patients in the cladribine tablets arm and two patients in the placebo arm died. The company did not consider that the deaths were related to the treatment administered during the trial.

Treatment emergent adverse events of special interest

The company has selected lymphopenia, infections and infestations, and malignancies as being TEAEs of special interest in the CLARITY trial and discusses these in Section B.2.10.1.3 of the CS.

Lymphopenia

The company claims that the higher rate of lymphopenia recorded in the cladribine tablets arm compared to the rate in the placebo arm (21.6% versus 1.8% is consistent with the mechanism of action of cladribine tablets. The company states that only four (0.5%) patients in the cladribine tablets arm discontinued treatment due to lymphopenia and, that at the end of the trial, eight (0.9%) patients in the cladribine tablets arm had Grade ≥3 lymphopenia. However, at further follow-up, the lymphocyte count for these eight patients had improved to Grade 0 or Grade 1.

Infections and infestations

The company briefly discusses the incidence of infections and infestations in the cladribine tablets arm and in the placebo arm (47.7% versus 42.5%); the company states that most of these infections occurred in the upper respiratory tract. The company reports that infection with herpes was 'common' in the cladribine tablets arm of the trial and that most cases were moderate to severe. Except for one case of herpes oticus, the herpes infections were successfully treated.

Malignancies

Three patients in the cladribine tablets arm of the CLARITY trial developed isolated malignancies: malignant melanoma, ovarian carcinoma and metastatic pancreatic carcinoma. The ERG notes from the EMA report[14] provided by the company that the EMA has concluded that there is no conclusive evidence of an increased risk of malignancies in people with MS who are treated with cladribine tablets. The EMA opinion is based on the results of the integrated safety analysis conducted by the company and presented in the CS.

ERG summary of adverse events in the CLARITY trial

Clinical advice to the ERG is that in NHS clinical practice, lymphopenia is associated with treatment with DMTs. Lymphopenia is an issue if it leads to infection; however, the risk of

infection in the CLARITY trial appears to be similar to the risks associated with other DMTs used in the NHS.

4.6 ERG critique of the indirect evidence

The company performed a series of NMAs to establish the comparative effectiveness of cladribine tablets versus relevant comparator treatments across the subpopulations relevant to the NICE scope.

4.6.1 Trials identified for inclusion in the network meta-analysis

The company conducted a systematic literature review (SLR) to identify RCTs which assessed the efficacy, HRQoL, safety and tolerability outcomes associated with key interventions in the treatment of RRMS. Further details of the SLR including inclusion and exclusion criteria and study selection can be found in Appendix D.1.1.1 and Appendix D.1.1.2 of the CS and Section 4.1 of this report.

As per the SLR inclusion criteria, the included RCTs recruited adult participants (≥18 years) with a confirmed diagnosis of RRMS. Some of the studies included within the SLR also included a small number of participants with progressive disease. The company excluded trials with more than 20% of progressive participants from the SLR and so included only studies with a minimum of 80% of participants with RRMS. Five trials,[48-52] with up to 12.3% of participants included in each trial, had progressive disease and none of these trials reported results separately for the RRMS only population. Therefore, a small proportion of the patients included within the NMAs had progressive MS rather than RRMS and this should be taken into consideration when interpreting results from networks that include one or more of these five trials.[48-52]

Table 27 provides a summary of the number of trials, participants, participant years and events (where applicable) contributing to the NMA for the key efficacy outcomes for the ITT population and for the three post-hoc subgroups.

Trial specific summary results and treatment networks for key efficacy outcomes (i.e., ARR, 3-month CDP at 24 months and 6-month CDP at 24 months) are provided in Appendix 10.2 of this ERG report. Trial-specific summary results for other efficacy outcomes, HRQoL outcomes and AEs can be found in Appendix A of the company response to the ERG clarification letter.

Table 27 Summary of trials and participants contributing to NMAs

Outcome	Analysis population	Number of trials	Number of participants / person years	Number of events
Efficacy outcomes				
ARR	ITT	39	36,863 person years	14,051
ARR hospital treated	ITT	10	15,005 person years	1552
ARR requiring steroid treatment	ITT	14	18,718 person years	4876
3-month CDP at 24 months	ITT	16	12,496 participants	2588
6-month CDP at 24 months	ITT	18	13,440 participants	1902
Relapse-free at 12 months	ITT	29	21,556 participants	14,676
Relapse-free at 24 months	ITT	24	15,191 participants	8813
NEDA-3 at 24 months	ITT	5	3874 participants	1924
ARR	HDA-RRMS	11	Not provided	Not provided
3-month CDP at 24 months	HDA-RRMS	6	Not provided	Not provided
6-month CDP at 24 months	HDA-RRMS	3	Not provided	Not provided
6-month CDP at 24 months at any time point	HDA-RRMS	4	Not provided	Not provided
Relapse-free at 24 months	HDA-RRMS	4	1169 participants	654
ARR	RES-RRMS	10	Not provided	Not provided
3-month CDP at 24 months	RES-RRMS	4	Not provided	Not provided
6-month CDP at 24 months	RES-RRMS	4	476 participants	80
ARR	SOT-RRMS	3	Not provided	Not provided

HRQoL and adverse event outcomes				
EQ-5D at 12 months	ITT	3	1285 participants	NA
EQ-5D at 24 months	ITT	5	5047 participants	NA
EQ-5D VAS at 12 months	ITT	4	3608 participants	NA
EQ-5D VAS at 24 months	ITT	4	3222 participants	NA
Study withdrawals (all cause)	ITT	39	22,617 participants	3633
Treatment withdrawals (all cause)	ITT	26	17,094 participants	3277
Study withdrawals (due to AEs)	ITT	28	19,967 participants	890
Treatment withdrawals (due to AEs)	ITT	31	20,596 participants	1294
Any AE	ITT	23	16,880 participants	14,484
Any SAE	ITT	28	19.917 participants	2639
Any TRAE	ITT	4	2886 participants	1582
Any grade 3/4 AE	ITT	3	2681 participants	235
Any cardiovascular events	ITT	4	3242 participants	138
Any infection	ITT	18	12,279 participants	5959
Any serious infection	ITT	7	5808 participants	144
Depression	ITT	19	12,001 participants	1234
ALT increased	ITT	20	13,291 participants	1538

AE=adverse event; ALT=alanine aminotransferase; ARR=annualised relapse rate; AST=aspartate aminotransferase; CDP=confirmed disability progression; EQ-5D=EuroQol 5 dimension questionnaire; HDA=high disease activity; HRQoL=health-related quality of life; ITT=intention-to-treat; RES=rapid evolving severe; RRMS=relapsing remitting multiple sclerosis; SAE=serious adverse event; SOT=sub-optimal therapy TRAE=treatment-related adverse events; VAS=visual analogue scale
Source: Appendix A, company response to ERG clarification letter

The ERG has produced weighted networks from the summary information for each NMA provided by the company to allow for assessment of the relative amount of information available for treatment comparisons in the network. The ERG notes that the networks displayed in Figure 5, Figure 6, Figure 11, Figure 12 and Figure 13 in Appendix 10.2 of this ERG report include previously unpublished data from the PRISMS trial,[43] this trial was also sponsored by the company, to allow the connection of cladribine tablets to alemtuzumab (via INF-β-1a Rebif 44 µg) for the ITT population, HDA-RRMS and RES-RRMS subgroups. The company notes that even when making use of unpublished data, it was not possible to connect cladribine tablets to alemtuzumab in the SOT-RRMS subgroup (see Figure 7 in Appendix 10.2 of this ERG report).

The company used funnel plots and contour-enhanced funnel plots to assess the possibility of publication bias for the following outcomes: qualifying ARR, 3-month CDP at 24 months and 6-month CDP at 24 months (CS, Appendix D, Figure 3, Figure 4 and Figure 5). The company concludes that the possibility of publication bias is unlikely. The ERG agrees with this interpretation and did not identify any additional trials that met the company's eligibility criteria (i.e., adults with RRMS) for inclusion in the network.

The ERG notes that the company did not provide information about the number of participants (or participant years) contributing to the NMAs of the key efficacy outcomes for the post-hoc subgroups, except for 6-month CDP at 24 months in the RES-RRMS subgroups. Furthermore, the ERG is unable to extract the participant numbers or the definitions used in the trials for the RES-RRMS and SOT-RRMS subgroups from the published literature of all of the trials. It is difficult for the ERG to fully interpret NMA results from the subgroups without details of the subgroup definitions and number of participants contributing to them. Therefore, the ERG assessments of the NMA results are made based on the relative precision of the summary results provided for the subgroups (i.e. the standard errors of the summary rate ratios or HRs, see network plots presented in Appendix 11.2 of this ERG report).

4.6.2 Methodological approach to the indirect comparison and/or multiple treatment comparison

The company intended to perform an NMA on all populations of interest where data were available (ITT, HDA-RRMS, RES-RRMS and SOT-RRMS) for several efficacy, safety tolerability and HRQoL outcomes. See Table 27 of this ERG report for a full list of outcomes considered by the company.

Data sources used within the NMAs were obtained from the published clinical literature, and from unpublished study reports for the CLARITY and PRISMS[43] trials. The company performed NMAs using a hierarchical Bayesian approach with Markov Chain Monte Carlo (MCMC) techniques using the statistical package WinBUGS.

A summary of the methodological and statistical approach of taken by the company for the NMAs is provided in Table 28.

The company presents NMA results from a random-effects (RE) model for all efficacy outcomes analysed in the ITT population, except for NEDA-3, where results are presented from a fixed-effects (FE) model. NMA results were presented from a FE model for efficacy outcomes from the HDA-RRMS, RES-RRMS and SOT-RRMS subgroups due to the limited number of studies contributing to the evidence networks. NMA results were presented from a mixture of FE or RE models depending on the number of studies contributing to NMA for HRQoL and AEs (see Appendix E of company response to ERG clarification letter for further details).

The ERG acknowledges that fitting RE models within small networks is difficult and agrees that the use of FE models may have been appropriate for the subgroups. However, as baseline characteristics, inconsistency and heterogeneity measures within the post-hoc subgroups are not available, the ERG notes that it is difficult to judge whether important statistical

inconsistency or heterogeneity is present within the results for the subgroups; hence, it is difficult to interpret the numerical NMA results within the subgroups.

Table 28 summarises the ERG's assessment of the methodological and statistical approaches used for the NMAs conducted by the company.

Table 28 ERG assessment of methodological and statistical approaches used for the NMAs

Component	Statistical approach with ERG comments
NMA model choice	ARR was analysed as a Poisson outcome with the total number of relapses observed within a treatment group and the total number of person-years of follow-up for that treatment group as the input data. CDP outcomes (3-month CDP and 6-month CDP at 24 months) were analysed as time-to-event outcomes, assuming an exponential distribution with participants having CDP sustained for 3 months defined as event within a treatment group and the total number of participants randomised for that treatment group defined as input data adjusted for study duration. Further details of the methodological approach and the approach for other efficacy outcomes, safety tolerability and health-related quality of life outcomes can be found in Appendix D 1.1.4.4 of the CS and in the company response to the ERG clarification letter. The ERG considers that the modelling of each outcome in NMA was appropriate
Arm-based or contrast-based NMA model	The company stated that an arm-based model was used rather than a contrast-based model was used to estimate the HRs and relative ARR to increase the amount of evidence contribution in the NMA and that these analyses were validated by comparing HRs and relative ARR reported across the studies contributing to the analysis versus posterior estimates from the NMA. The ERG acknowledges the rationale of the company for employing an arm-based approach but notes the potentially serious limitations of this approach, such as biases in the resulting relative treatment effects due to over-inflated posterior variances and difficulties in translating relative effects from such approaches to predictions of new absolute or relative effects.[53]
NMA model validation	In order to further validate the output of the NMA, anchor based indirect treatment comparisons based on the methods of Bucher et al[54] and a Frequentist approach to NMA was also performed via a generalised linear mixed model (GLMM) approach. The company states that the findings from these two validation analyses were in line with the Bayesian NMA. The ERG agrees that validation of results via a range of methodological approaches is advisable, results of validation were not provided to the ERG so the ERG cannot comment on the robustness of results

Component	Statistical approach with ERG comments
Investigation of heterogeneity	In response to the ERG clarification letter, the company provided results of meta-regression analyses that had been conducted to investigate the impact of baseline characteristics on heterogeneity; the ERG assumes the results provided were from analyses conducted in the ITT population. No significant associations between baseline characteristics and the outcome were found for most of the efficacy outcomes (i.e., 3-month or 6 month CDP or proportion of participants remaining relapse-free) but for ARR, significant associations with EDSS score and percentage of females were found. The company states that as effect size and credible intervals for EDSS and percentage female were close to 0, it is unlikely that this difference would translate into any clinical relevance. The ERG agrees that this statement is a reasonable judgement. The company states that both fixed-effects (FE) and random-effects (RE) models were considered for NMAs and that the choice of FE versus RE model was based on the relative goodness of fit of the models, using residual deviance and the deviance information criterion (DIC). The model with lowest DIC and/or the closest total residual deviance to the number of data points in the model was considered the best fitting model. The ERG considers that the DIC is a measure of model fit rather than of statistical heterogeneity and that choices between FE and RE models within an NMA should be made taking into account consistency of trial designs, populations and evidence sources, rather than solely on model fit. In response to the ERG clarification letter, the company provided between-study standard deviation values from RE NMA models in the ITT population as a measure of heterogeneity.
Investigation of inconsistency	Inconsistency within closed loops of the network was investigated via inconsistency factors to test the consistency between direct and indirect results that contributed to the NMA analysis.[55] In response to the ERG clarification letter, the company provided results of all tests of inconsistency for efficacy outcomes for the ITT population and found no significant evidence of inconsistency within results for the key efficacy outcomes (i.e., ARR, 3-month CDP at 24 months and 6-month CDP at 24 months). Potential inconsistency was found for one loop for the proportion of participants relapse-free at 12 months, therefore the ERG suggests that results of this NMA should be interpreted with caution. The ERG considers this approach to investigating inconsistency to be appropriate but notes that it was unclear whether any inconsistency was present in results for the NMAs of the post-hoc subgroups (where closed loops were present).

ARR=annualised relapse rate; CDP=confirmed disability progression; DIC=deviance information criterion; EDSS=expanded disability status scale; ERG=evidence review group; FE=fixed-effects; HR=hazard ratio; ITT=intention-to-treat; NMA=network meta-analysis; RE=random-effects
Source: CS, Appendix D, company response to ERG clarification letter and ERG comment

4.6.3 Characteristics of trials included in the network meta-analysis

Trial design and participant characteristics of the CLARITY trial are presented in Section 4.2.2 and Section 4.2.3 respectively of this ERG report. General trial design characteristics are presented in Appendix D.1.1.4.1 of the CS, inclusion and exclusion criteria of the trials are presented in Appendix D.1.1.4.2 of the CS and participant characteristics are presented in Appendix D.1.1.4.3 of the CS.

The ERG notes that all participant characteristics presented within the CS relate to the ITT populations of the trials and that demographic information within the post-hoc subgroups (HDA-RRMS, RES-RRMS, SOT-RRMS) is not presented. Therefore, considerations of variability of participant characteristics and the additional analyses conducted to investigate the impact of baseline characteristics on the outcomes of the NMAs apply to the ITT population only and do not necessarily translate to the post-hoc subgroups.

Participant populations were generally quite similar across the trials included in the NMAs, however demographic information was frequently omitted from published trial reports, particularly regarding ethnicity. The mean age by treatment arm across trials ranged from 27.4 to 40.7 years. All trials (except for one treatment arm in one trial[56]) recruited more females than males, with the proportion of females ranging from 33.3 to 78.95% across treatment arms across trials.

The most variability was observed in the mean disease duration at baseline, ranging from 1 to 10.3 years across treatment arms across trials and EDSS score which was reported in a variety of ways across studies (mean and standard deviation, median and range etc.) and makes comparing this characteristic across arms across trials difficult. Overall, the mean or median EDSS score was between 2 and 3 for the majority of treatment arms across trials.

The company acknowledges the uncertainty around disease duration and EDSS score and conducted meta-regression analyses considering these characteristics and other baseline characteristics as sources of heterogeneity in the analysis (see Section 4.6.2 of this ERG report for further discussion).

The company also conducted sensitivity analyses to evaluate the impact of study characteristics on the results of the NMA based on blinding, diagnostic criteria, year of publication and study phase. Further details of these sensitivity analyses for the key efficacy outcomes (i.e., ARR, 3-month CDP at 24 months and 6-month CDP at 24 months) are provided in Appendix 10.3 of this ERG report and sensitivity analysis results for other efficacy outcomes and tolerability outcomes are provided in Appendix B of the company response to the ERG clarification letter.

The company states that the definition of relapse was subject to slight variation but that '…it was commonly defined as new or worsening symptoms that last 24 hours and occurs in the absence of fever or infection' (CS, Appendix D, Table 7). The company also states that the definition of CDP varied between trials but that '…it was commonly defined as at least 1 point EDSS increase, or a 0.5 point increase if the baseline EDSS was ≥ 5.5, confirmed during two subsequent neurological examinations separated by an interval of at least three to six months free of relapses.' (CS, Appendix D, Table 7). The ERG notes that variation in outcome definitions should be taken into account when interpreting the results of the NMAs.

The ERG considers that the trial designs and participant characteristics are broadly similar and that the additional sensitivity analyses undertaken by the company to examine areas of uncertainty in trial design and baseline characteristics (particularly disease duration and EDSS

score) are appropriate. The ERG does not consider that the observed differences across the trials would violate the assumption of transitivity required for the inclusion of these trials in the same network. The ERG also considers that presenting results from a RE model for the ITT population which takes account of statistical heterogeneity arising from variation across trials was an appropriate approach taken by the company. However, the ERG is uncertain whether presenting results from a FE model (rather than from an RE model) for the post-hoc subgroups was the most appropriate approach (see Section 4.6.2 of this ERG report for further discussion).

4.6.4 Assessment of risk of bias of the trials included in the network meta-analysis

The company performed an assessment of study quality and risk of bias using the NICE checklist[31] for all trials included in the NMAs. Detailed information for each domain of quality can be found in Appendix D.1.1.3 and Appendix D.1.1.4 of the CS. A summary of the risk of bias domains is also provided in Appendix 10.4 of this ERG report.

Overall, the ERG agrees with the quality assessments made by the company and notes that the majority of trials included within at least one NMA were generally of good quality. However, important design information was omitted from some trial publications relating to methods of randomisation, allocation concealment and blinding and that the possibility of selective reporting bias could not be excluded from over a third of included trials.

4.6.5 Results from the indirect comparison and/or multiple treatment comparison

Summary results for key efficacy outcomes

A summary of NMA results for cladribine tablets versus the comparators of interest is presented in Table 29 for the key efficacy outcomes for the ITT population and for the three post-hoc subgroups.

The ERG notes that Table 29 clearly demonstrates the paucity of comparative data for cladribine tablets versus the comparators of interest within all three post-hoc subgroups, particularly for the outcomes of 3-month CDP at 24 months and 6-month CDP at 24 months for which no comparative data are available for the SOT-RRMS subgroup.

Summary NMA results for the proportion of participants remaining relapse-free at 12 months and 24 months and the proportion of participants with no evidence of disease activity (NEDA-3) at 24 months in the ITT population are presented in Table 11 of Appendix D of the CS. Summary NMA results for the proportion of participants remaining relapse-free at 24 months

in the HDA-RRMS subgroup are presented in Table 11 of Appendix D of the CS. No further efficacy outcomes could be evaluated in the NMAs for the RES-RRMS and SOT-RRMS subgroups.

Herein, this section of this ERG report focusses mainly on the RES-RRMS and SOT-RRMS subgroups as these subgroups contribute efficacy data to the economic analyses.

Table 29 Summary of efficacy NMA results between cladribine tablets 3.5 mg/kg and comparators for ITT population and post-hoc subgroups

Cladribine tablets 3.5 mg/kg versus	ARR				3-month CDP at 24 months				6-month CDP at 24 months			
	ITT	HDA	RES	SOT	ITT	HDA	RES	SOT	ITT	HDA	RES	SOT
Placebo	↑	↑	↑	↑	↑	↑	↑	-	↑	↑	↑	-
Alemtuzumab12 mg, qd	↓	↔	↓	-	↓	-	-	-	↓	↑	↑	-
Daclizumab HYP 150 mg, q4w	↔	-	↑	-	↔	-	-	-	↔	-	-	-
DMF, 240 mg, bid	↑	↑	-	-	↔	↑	-	-	↑	-	-	-
Fingolimod, 0.5mg, qd	↔	↔	↑	↔	↑	↑	↔	-	↑	-	-	-
GA, 20 mg, qd	↑	↑	-	-	↑	↑	-	-	↑	-	-	-
GA, 40 mg, tiw	↑	-	-	-	-	-	-	-	-	-	-	-
IFN-β-1a, 30 µg, q1w	↑	↑	↑	↑	↑	-	-	-	↑	-	-	-
PEG IFN beta-1a, 125 µg, q2w	↑	-	-	-	-	-	-	-	-	-	-	-
IFN-β-1a, 22 µg, tiw	↑	-	-	-	↔	-	-	-	-	-	↑	-
IFN-β-1a, 44 µg, tiw	↑	-	↑	-	↔	-	-	-	↑	↑	-	-
IFN-β-1b, 250 µg, eod	↑	-	-	-	↑	-	-	-	↓	-	-	-
Natalizumab, 300 mg, q4w	↓	↓	↓	-	↓	-	↓	-	↓	-	↓	-
Teriflunomide, 7 mg, od	↑	↑	↑	-	↑	-	↓	-	↑	-	-	-
Teriflunomide,14 mg, od	↑	↑	↑	-	↑	-	↓	-	↑	-	-	-

ARR=annualised relapse rate; bid=twice a day; CDP=confirmed disability progression; DMF=dimethyl fumarate; GA=glatiramer acetate; HDA=high disease activity; HYP=high yield process; IFN=Interferon; µg=microgram; mg=milligram; od=once daily; qd=per day; q1w=once weekly; q4w=every 4 weeks; RES=rapidly evolving severe; SOT=sub-optimal therapy
Source: CS, Appendix D, adapted from Table 11, Table 12 and Table 13

↑ Indicates better efficacy for cladribine tablets 3.5 mg/kg; ↓ indicates lower efficacy for cladribine tablets 3.5 mg/kg; "↔" indicates equivalent efficacy of cladribine tablets 3.5 mg/kg and comparator; cells highlighted in green represent statistically significant results in favour of cladribine tablets 3.5 mg/kg; "-" indicates that NMA was not feasible against these interventions, either due to lack of connections within the networks or due to lack of studies. Highlighted represent statistically significant results in favour of cladribine tablets

A random-effects model was applied to NMA for the ITT population and a fixed-effects model was applied to NMA for the HDA-RRMS, RES-RRMS and SOT-RRMS subgroups

The ERG also notes one discrepancy between Table 12 and Table 15 (CS, Appendix D) for the results of 3-month CDP at 24 months in the HDA-RRMS subgroup. The former table of summary results indicates a statistical advantage to fingolimod 0.5 mg qd, while the latter table of narrative results indicates a statistical advantage to DMF 240 mg bid. The ERG assumes that Table 12 (CS, Appendix D) contains a typographical error and this error has been corrected in Table 16 of this ERG report

NMA results for qualifying annualised relapse rate

Table 30 presents the numerical NMA results for ARR for the ITT population and the three post-hoc subgroups. When interpreting results, the company defines a (non-statistically significant) 'numerical advantage' as a rate ratio or HR of less than 0.9 or greater than 1.1 and 'similar results' as a rate ratio or HR between 0.9 and 1.1. The ERG agrees that these interpretations are appropriate.

In the ITT population, cladribine tablets were associated with a statistically significantly greater reduction in ARR compared with placebo and many other comparators (see Table 30). A numerical advantage was observed for alemtuzumab and natalizumab over cladribine tablets although the advantage was not statistically significant. Where data were available, comparisons in the HDA-RRMS subgroup were generally consistent with comparisons in the ITT population, with the exception that alemtuzumab was numerically comparable to cladribine tablets in the HDA-RRMS subgroup.

In the RES-RRMS subgroup, cladribine tablets were statistically significantly better than placebo, IFN-β-1a 30 µg, and teriflunomide 14 mg. Cladribine tablets were also numerically better than daclizumab, fingolimod, INF-β-1a (Rebif 44 µg) and teriflunomide 7 mg while alemtuzumab and natalizumab were numerically better than cladribine tablets; however, none of these numerical advantages was statistically significant. In the SOT-RRMS subgroup, cladribine tablets were numerically better than placebo and IFN-β-1a 30 µg q1w, and comparable to fingolimod; none of these results were statistically significant.

The company argues that the results for cladribine tablets against alemtuzumab should be interpreted with caution due to heterogeneity between the studies assessing alemtuzumab; CARE-MS I (CAMMS323)[57], CARE-MS II (CAMMS423)[58] and CAMMS223.[59] The company notes key differences between these studies with respect to study phase, eligibility criteria (McDonald 2001[60] or McDonald 2005[61]), baseline EDSS, treatment history, and the onset of disease symptoms and notes the high risk of bias due to the open-label assessment in CARE-MS II trial.[58]

The ERG agrees that NMA results should be interpreted with caution where heterogeneity is considered to be present due to differences in designs and participant characteristics within the trials included in the network. The ERG also notes that any heterogeneity present in the network will impact on all comparisons made in the NMA, therefore all NMA results should be interpreted with caution rather than just the comparison of cladribine tablets against alemtuzumab.

Table 30 NMA results for ARR for cladribine tablets 3.5m g/kg versus comparators for ITT population and subgroups (random-effects model)

Cladribine tablets 3.5 mg/kg versus	ITT		HDA-RRMS		RES-RRMS		SOT-RRMS
	Median RR (95% CrI)	Mean (SD)	Median RR (95% CrI)	Mean (SD)	Median RR (95% CrI)	Mean (SD)	Median RR (95% CrI)
Placebo	0.42 (0.32 to 0.54)	0.42 (0.05)	0.35 (0.24 to 0.51)	0.36 (0.07)	[redacted]	[redacted]	[redacted]
Alemtuzumab, 12 mg, qd	1.31 (0.95 to 1.82)	1.32 (0.22)	0.99 (0.59 to 1.66)	1.02 (0.27)	[redacted]	[redacted]	-
Daclizumab HYP, 150 mg, q4w	0.92 (0.67 to 1.26)	0.94 (0.15)	-	-	[redacted]	[redacted]	-
DMF, 240 mg, bid	0.79 (0.58 to 1.08)	0.8 (0.13)	0.66 (0.41 to 1.06)	0.68 (0.17)	-	-	-
Fingolimod, 0.5 mg, qd	0.91 (0.68 to 1.23)	0.92 (0.14)	0.95 (0.58 to 1.54)	0.98 (0.25)	[redacted]	[redacted]	[redacted]
GA, 20 mg, qd	0.64 (0.49 to 0.85)	0.65 (0.09)	0.44 (0.25 to 0.76)	0.46 (0.13)	-	-	-
GA, 40mg, tiw	0.62 (0.44 to 0.88)	0.63 (0.11)	-	-	-	-	-
IFN-β-1a, 22 µg, tiw	0.58 (0.43 to 0.81)	0.59 (0.10)	-	-	-	-	-
IFN-β-1a, 30 µg, q1w	0.52 (0.40 to 0.69)	0.53 (0.07)	0.49 (0.27 to 0.89)	0.52 (0.16)	[redacted]	[redacted]	[redacted]
IFN-β-1a, 44 µg, tiw	0.64 (0.48 to 0.84)	0.64 (0.09)	0.49 (0.31 to 0.78)	0.50 (0.12)	[redacted]	[redacted]	-
IFN-β-1b, 250 µg, eod	0.62 (0.47 to 0.84)	0.63 (0.09)	-	-	-	-	-
Natalizumab, 300 mg, q4w	1.24 (0.89 to 1.71)	1.25 (0.20)	1.14 (0.70 to 1.84)	1.17 (0.29)	[redacted]	[redacted]	-
PEG IFN beta-1a, 125 µg, q2w	0.63 (0.44 to 0.92)	0.65 (0.12)	-	-	-	-	-
Teriflunomide, 14 mg, od	0.63 (0.47 to 0.84)	0.63 (0.09)	0.63 (0.38 to 1.05)	0.65 (0.17)	[redacted]	[redacted]	-
Teriflunomide, 7 mg, od	0.55 (0.40 to 0.73)	0.55 (0.08)	0.51 (0.31 to 0.84)	0.53 (0.13)	[redacted]	[redacted]	-

bid=twice a day; CrI=credible interval; DMF=dimethyl fumarate; eod=every other day; GA=glatiramer acetate; HDA=high disease activity; HYP=high yield process; IFN=interferon; kg=kilogram; µg=microgram; mg=milligram; od=once daily; qd=per day; q1w=once a week; q4w=every 4 weeks; RES=rapidly evolving severe; RR=rate ratio; SD=standard deviation; SOT=suboptimal therapy; tiw=thrice a week
Source: CS, Appendix D, Table 14
Highlighted cells represent statistically significant results in favour of cladribine tablets 3.5 mg/kg
"-" indicates that NMA was not feasible against these interventions, either due to lack of connections within the networks or due to lack of studies
A random-effects model was applied to NMA for the ITT population and a fixed-effects model was applied to NMA for the HDA-RRMS, RES-RRMS and SOT-RRMS subgroups

NMA results for 3-month CDP sustained at 24 months

In both the ITT population and HDA-RRMS subgroup, at 24 months, cladribine tablets demonstrated a statistically significantly greater improvement compared with placebo in terms of 3-month CDP sustained for 3 months. In the HDA-RRMS subgroup, cladribine tablets were statistically significantly better than dimethyl fumarate (DMF) but there were no numerical or statistically significant differences between these treatments in the ITT population.

While numerically favourable results were observed with alemtuzumab and natalizumab compared with cladribine tablets in the ITT population, results in the HDA-RRMS subgroup numerically favoured cladribine tablets over natalizumab (comparisons versus alemtuzumab were not possible in the HDA-RRMS subgroup); although none of these results were statistically significant.

No comparative data were available to perform an NMA for 3-month CDP at 24 months in the RES-RRMS and SOT-RRMS subgroups.

As for the NMA of ARR, the company notes that the results for cladribine tablets against alemtuzumab should be interpreted with caution due to potential heterogeneity in the results of the alemtuzumab trials, due to the different phases, and because the comparison of cladribine tablets versus alemtuzumab was only feasible via bridging through two comparators i.e. INF-β-1a (Rebif 44µg) and INF-β-1a (Rebif 22µg). The ERG agrees with the company that these results should be interpreted cautiously, and notes that heterogeneity in the network will impact upon all comparisons therefore these results should also be interpreted with caution.

NMA results for 6-month CDP sustained at 24 months

Cladribine tablets were statistically significantly better than placebo and IFN beta-1a 44 µg in the HDA-RRMS subgroup. Cladribine tablets did not show a statistically significant advantage over any comparator.

Although, the NMA results in the ITT population numerically favoured alemtuzumab and natalizumab over cladribine tablets, in the HDA-RRMS group, cladribine tablets were numerically better than alemtuzumab (comparisons versus natalizumab were not possible in the HDA-RRMS subgroup).

In the RES-RRMS population, comparisons were only possible versus alemtuzumab, IFN-β-1a 44 µg, and natalizumab. Cladribine tablets were numerically better than placebo and IFN-β-1a 44 µg, and alemtuzumab and natalizumab were numerically better than cladribine tablets. None of these numerical advantages were statistically significant.

The company notes that the results for cladribine tablets against alemtuzumab should be interpreted with caution 'due to across trial differences between the studies assessing alemtuzumab 12 mg qd' (CS, Appendix D.1.1.1.6). In line with the NMA results for ARR and 3-month CDP at 24 months, the ERG notes that heterogeneity in the network will impact upon all comparisons, therefore all results should be interpreted with caution rather than just the cladribine tablets versus alemtuzumab results.

No comparative data were available to perform an NMA for this outcome in the SOT-RRMS subgroup.

NMA results for quality of life, tolerability and safety outcomes

NMAs were performed only within the ITT population for HRQoL, safety and tolerability; no comparative data for the three post-hoc subgroups were available for NMA.

Therefore this ERG report refers only briefly to these NMA results and further details can be found in Table 17 (CS, Appendix D) for HRQoL results including EQ-5D and ED-5D VAS at 12 months and 24 months, Table 18 (CS, Appendix D) for tolerability results including all cause or AE related study and treatment withdrawals, Table 19 and Table 20 (CS, Appendix D) for safety outcomes including adverse events (see Section 5.6.2 of this ERG report for a full list of safety outcomes reported). Clarification of which analyses were performed with an FE model and which were performed with an RE model are provided in Appendix E of the company response to the ERG clarification letter.

A limited number of HRQoL comparisons could be made using an NMA approach due to the available data (see Table 27). Few numerical or statistical differences were observed in HRQoL between cladribine tablets and available comparators.

Tolerability results were generally in favour of cladribine tablets except for alemtuzumab and IFN-β-1b 250 µg and a numerically lower proportion of treatment withdrawals due to AEs was observed with placebo compared with cladribine tablets.

No statistically significant difference was observed between cladribine tablets, placebo and comparators in terms of any AE, any SAE, and any Grade 3/4 AE. The risk of treatment-related AEs was significantly lower with cladribine tablets compared with INF-β-1a (Avonex) and INF-β-1a (Plegridy). However, the risk of any treatment-related AE was significantly higher in participants treated with cladribine tablets compared with placebo.

4.6.6 Additional assessment of indirect evidence

Uncertainties in the NMA

The company acknowledges that the paucity of data available to assess key efficacy outcomes in the subgroups listed in the NICE scope (particularly SOT-RRMS) is a limitation. In particular, it was challenging to compare alemtuzumab to other in-scope therapies in the RES-RRMS and SOT-RRMS populations via a classic NMA due to the lack of published data linking the control arm of the alemtuzumab studies, interferon beta-1a (IFN-β1a), to the network; see Section 4.6.1 of this ERG report and Appendix 10.1 of this ERG report for treatment networks.

Given the importance of the comparison with alemtuzumab in the UK, the company also conducted an additional meta-regression analysis for the outcome of 6-month CDP at 24 months with the aim of providing a more robust comparison between cladribine tablets and alemtuzumab, particularly in the SOT-RRMS population. The objective of the meta-regression was to estimate the efficacy of drug therapies in the RES-RRMS and SOT-RRMS subgroups, by relating efficacy to baseline risk, and centering baseline risk to the expected value in each group. Efficacy results estimated from this meta-regression for cladribine tablets compared to relevant comparators of interest for each subgroup are included in the company's economic analyses of 6-month CDP at 24 months.

The evidence network for the meta-regression is provided in Figure 2 and a summary of the trial data used in the meta-regression analysis is provided in Table 31

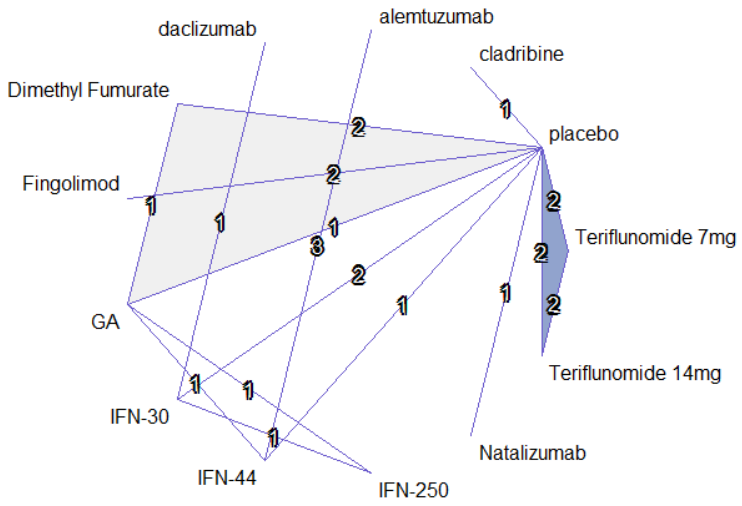

Figure 2 Evidence network for the meta-regression of 6-month CDP at 24 months

CDP=confirmed disability progression; IFN=interferon; GA=Glatiramer acetate
Source; CS, Appendix L, Figure 15

Table 31 Summary of the trials used in the meta-regression of 6 month CDP at 24 months

Study	Treatment 1	Event 1	Total 1	Treatment 2	Event 2	Total 2	Treatment 3	Event 3	Total 3	Number of arms
AFFIRM trial	Placebo	72	315	Natalizumab	69	627	NA	NA	NA	2
BECOME trial	Glatiramer acetate	6	39	IFN-β1a 250 mcg	4	36	NA	NA	NA	2
BRAVO trial	Placebo	46	450	IFN -β1a 44 mcg	35	447	NA	NA	NA	2
CAMMS223 trial	Alemtuzumab 12mg	4	113	IFN -β1a 44 mcg	19	111	NA	NA	NA	2
CARE-MS I trial	Alemtuzumab 12mg	30	386	IFN -β1a 44 mcg	21	195	NA	NA	NA	2
CARE-MS II trial	Alemtuzumab 12mg	54	436	IFN -β1a 44 mcg	43	231	NA	NA	NA	2
CONFIRM trial	Placebo	45	363	Dimethyl fumurate	28	362	Glatiramer acetate	38	360	3
Decide Trial	Daclizumab	83	919	IFN -β1a 30mcg	111	922	NA	NA	NA	2
DEFINE	Placebo	69	410	Dimethyl fumurate	52	411	NA	NA	NA	2
FREEDOMS II trial	Placebo	63	355	Fingolimod	49	358	NA	NA	NA	2
FREEDOMS trial	Placebo	79	418	Fingolimod	53	425	NA	NA	NA	2
INCOMIN trial	IFN -β1a 30mcg	28	92	IFN -β1a 250 mcg	13	96	NA	NA	NA	2
MSCRG trial	Placebo	50	143	IFN -β1a 30 mcg	35	158	NA	NA	NA	2
REGARD trial	Glatiramer acetate	33	378	IFN -β1a 44 mcg	45	386	NA	NA	NA	2
TEMSO trial	Placebo	68	363	Teriflunomide 14 mg	49	359	Teriflunomide 7 mg	51	366	3
TOWER trial	Placebo	46	389	Teriflunomide 14 mg	43	372	Teriflunomide 7 mg	61	408	3
CLARITY trial	Placebo	[redacted]	[redacted]	Cladribine tablets	[redacted]	[redacted]	NA	NA	NA	2
PRISMS trial (unpublished data)	Placebo	[redacted]	[redacted]	IFN -β1a 44 mcg	[redacted]	[redacted]	NA	NA	NA	2

CDP=confirmed disability progression; IFN–β=interferon beta; NA=not applicable
Source: CS, Appendix L, Table 60

Methods of the meta-regression analysis

The company conducted the meta-regression using guidance from the NICE DSU document TSD3,[62] using a similar methodological approach to the analysis of 6-month CDP at 24 months in the NMA (see Section 4.6.2 of this ERG report).

The ERG considers that the meta-regression methodology employed by the company was appropriate with regards to modelling of the interaction term (independent, exchangeable or common effects) and choice of fixed or random-effects meta-regression model

The ERG notes that the meta-regression approach outlined in the TSD3[62] document is used to explore treatment-covariate interactions, such as an interaction between treatment effect and baseline risk, as a source of heterogeneity. The company has used the approach outlined in TSD3[62] to model treatment-covariate interactions to allow baseline risk estimates to predict treatment effect estimates for specific subgroups. The ERG is uncertain whether the approach outlined in TSD3[62] is valid for the company's objectives.

Eleven of the trials included in the meta-regression (see Table 31) were placebo-controlled trials and informed the baseline risk adjustment. The baseline risk 6-month CDP in the placebo RES-RRMS group of CLARITY was [redacted].

The treatment effects obtained from the meta-regression model are the log-hazard ratios (drug versus placebo) at the mean baseline risk value. Analyses performed centred on the baseline risk of the SOT-RRMS subgroup of the CLARITY trial yielded similar estimates of the relationship between effect and baseline risk as the RES-RRMS analysis, therefore only the baseline risk for the RES-RRMS analysis was used to predict outcomes.

Results of the meta-regression analysis on baseline risk

The company presents numerical results from four meta-regression models (FE or RE, common or exchangeable covariates) in Table 61 of Appendix K of the CS.

The company notes that, in terms of model fit, i.e. the DIC and posterior means of the residual deviances, there is not one model that is clearly favoured (model DICs ranging from [redacted]) and that all four models generated equally plausible effect estimates based on these model fit statistics.

Therefore the company concludes that the simpler common covariate model was preferred to an exchangeable model and that while fixed and random effects models generate equally plausible fits top the data, as heterogeneity is expected across the studies included in the network, the random-effect with common covariate model was preferred.

The ERG agrees with the assessment of the company that this model is the most appropriate of the four regression models for the data and the context of the decision problem. Results of this model are presented within Table 32 of this ERG report.

The interpretation of the log HRs within Table 32 of this ERG report correspond to the effect of the comparator (cladribine tablets, alemtuzumab, daclizumab, fingolimod or natalizumab) versus placebo for participants with a baseline probability of progression that is equal to the mean progression probability in the RES-RRMS population of the CLARITY trial (and un-centred and transformed to produce treatment effect estimates for comparator versus placebo consistent with the baseline risk in the SOT-RRMS subgroup). As all comparisons within the meta-regression are made versus placebo, the comparator interventions are compared in terms of the numerical results and overlap of credible intervals.

Table 32 Log and normalised hazard ratios on 6-month CDP after centering on baseline risk of the RES-RRMS subgroup of the CLARITY trial

Treatment versus placebo	Log HR from the random-effect model with common covariate for baseline risk				Normalised HR (derived from log-HR and baseline risk) and 95% credible intervals	
	Mean	SD	L95%	U95%	Centred on RES-RRMS	Centred on SOT-RRMS
Cladribine tablets	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Daclizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fingolimod	[redacted]	[redacted]	[redacted]	[redacted]	Not applicable	[redacted]
Natalizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Not applicable
Between-study SD	[redacted]	[redacted]	[redacted]	[redacted]	Risk in RES-RRMS population of [redacted]	Risk in SOT-RRMS population of [redacted]
Baseline risk covariate	[redacted]	[redacted]	[redacted]	[redacted]		
Residual deviance	[redacted]					
pD	[redacted]					
DIC	[redacted]					

CDP=confirmed disability progression; DIC=deviance information criterion; HR=hazard ratio; L95%=lower bound of 95% credible interval; pD=effective number of parameters; RES=rapidly evolving severe; RRMS=relapsing-remitting multiple sclerosis; SD=standard deviation; SOT=sub-optimal therapy; U95%=upper bound of 95% credible interval
Source: CS, Table 70; company response to ERG clarification letter

Meta-regression results show that cladribine tablets were predicted to be more efficacious than fingolimod (log hazard ratio relative to placebo of [redacted] for cladribine tablets versus [redacted] for fingolimod) and alemtuzumab ([redacted] versus [redacted]), but marginally less efficacious than natalizumab ([redacted] versus [redacted]) and daclizumab ([redacted] versus [redacted]).

Within the company decision problem (CS, Table 2), fingolimod was not specified as a comparator to cladribine tablets within the RES-RRMS subgroup and natalizumab was not

specified as a comparator to cladribine tablets within the SOT-RRMS subgroup. Therefore normalised HRs are not calculated for these comparisons.

Within the RES-RRMS subgroup, the corresponding normalised HRs were [redacted] for treatment effect of cladribine tablets, [redacted] for alemtuzumab, [redacted] for daclizumab, in the RES-RRMS and [redacted] for natalizumab versus placebo. Within the SOT-RRMS subgroup the corresponding normalised HR in this population were [redacted] for cladribine tablets, [redacted] for alemtuzumab, [redacted] for daclizumab, and [redacted] for fingolimod versus placebo.

The company concludes that the meta-regression predicted that all comparators are less effective in the SOT-RRMS subgroup than in RES-RRMS subgroup and, due to the significant overlap in the credible intervals across all comparisons, no therapy statistically dominates in terms of efficacy.

Validation of the meta-regression analysis

The company notes that the meta-regression model has two assumptions; firstly that baseline risk is predictive of effect size (on a linear scale, given that the meta-regression model is expressed on a complimentary log-log scale) and that the relationship between baseline risk and effect size explains the effects observed in the different subgroups (i.e. that any differences across subgroups are not due to other known or unknown factors).

The company validates the first assumption by plotting the log HR of each comparator compared to placebo versus baseline risk complimentary log-log scale and concludes that there is evidence of a consistent linear relationship between baseline risk and effect size for fingolimod, natalizumab and cladribine tablets (CS, Appendix K, Figure 16) and that the comparable slopes of these trend lines indicate that the relationship between effect size and baseline risk may also be consistent across drugs. The ERG agrees in principle with this interpretation but notes that evidence of a linear relationship is not consistent for all comparators within the meta-regression.

The company validates the second assumption by considering whether results produced by the meta-regression are sufficiently predictive of the subgroup effect sizes observed in individual studies (the CLARITY, AFFIRM[63], and PRISMS[43] trials), when un-centred and transformed to the corresponding baseline risks. Table 33 shows the predicted compared to the observed mean HR for the RES-RRMS subgroup for the relevant comparison of each trial. The company concludes that for the CLARITY and PRISMS[43] trials, the observed effect size has been accurately predicted by the meta-regression but for the natalizumab versus placebo

comparison from the AFFIRM[63] trial that the effect size has been under-estimated, with a predicted hazard ratio of [redacted] (observed).

Table 33 Predicted versus observed mean HR for RES-RRMS subgroup in the CLARITY, AFFIRM, and PRISMS trials

Therapy (vs placebo)	Study	Baseline risk in placebo group	Predicted effect size (mean hazard ratio)	Observed effect size (mean hazard ratio)
Cladribine tablets	CLARITY	[redacted]	[redacted]	[redacted]
Natalizumab	AFFIRM	[redacted]	[redacted]	[redacted]
Interferon beta-1a 44mcg	PRISMS	[redacted]	[redacted]	[redacted]

Source: adapted from CS, Appendix K, Table 64

The ERG suggests that the results presented within Table 33 of this ERG report may indicate that the relationship between baseline risk and effect size does not explain the differences observed across subgroups, hence the meta-regression approach may be invalid.

The company suggests that under-estimation may be due to the relationship between baseline risk and effect size estimate in the AFFIRM[63] trial differing between the relationship between baseline risk and effect size in other studies, including the CLARITY and PRISMS[43] trials. This suggestion contradicts the company's interpretation of their first validation (i.e., that the similar slope trend lines of natalizumab and cladribine tablets indicate that the relationship between effect size and baseline risk may also be consistent across drugs).

Due to the ERG's previously outlined concerns regarding the validation results presented by the company and uncertainty regarding whether the meta-regression approach is applicable to the objective of the company in this analysis, the ERG encourages caution when interpreting the results of this meta-regression.

4.7 Conclusions of the clinical effectiveness section

Direct clinical evidence

The direct clinical effectiveness evidence for cladribine tablets versus placebo was derived from the CLARITY trial. The ERG highlights the following points:

- The CLARITY trial was of good quality and was well conducted; participant characteristics were balanced across the treatment groups and the pre-planned statistical methods were generally appropriate.
- The clinical effectiveness evidence presented within the CS is mainly based upon three subgroups of participants that were defined post-hoc. In addition, three post-hoc outcomes were presented within the CS that were not included in the original analysis of the CLARITY trial. The ERG acknowledges the company rationale was necessary for defining subgroups and outcomes to address the NICE Decision Problem, but notes

the inherent limitation of reduced statistical power when conducting post-hoc analyses, particularly within smaller subgroups than originally defined within the CLARITY trial.

- The company amended their statistical approach with regards to missing data from the original analysis of the CLARITY trial for the re-analysis presented within the CS; the ERG agrees that the statistical approach used within the re-analysis is more appropriate than the original approach.
- Results of the pre-planned primary outcome show relative numerical reductions in qualifying ARR for cladribine tablets compared to placebo in the ITT population and in the three post-hoc subgroups. These results were statistically significant for the ITT population, HDA-RRMS and RES-RRMS subgroups but not for the SOT-RRMS subgroup.
- Results of pre-planned and post-hoc efficacy outcomes relating to relapse and disability progression generally show numerical advantages to cladribine tablets compared to placebo and the advantages within the subgroups tend to be numerically larger compared to the results within the ITT population. For secondary outcomes relating to relapse, these numerical advantages are significant within the ITT population, HDA-RRMS and RES-RRMS subgroups but not for the SOT-RRMS subgroup. For secondary outcomes relating to disability progression, these numerical advantages are significant within the ITT population and HDA-RRMS subgroup but not for the RES-RRMS and SOT-RRMS subgroups.
- Results of a post-hoc efficacy composite outcome NEDA-3, defined as no evidence of disease activity, showed numerically and statistically significant advantages for cladribine tablets compared to placebo in the ITT population and in all three post-hoc subgroups. The ERG advises caution when interpreting these results, due to the post-hoc nature of the analyses and the small participant numbers within the subgroups.

Indirect clinical evidence

Regarding the NMAs, the ERG considers that the general approach of the company is appropriate with regard to:

- The identification of trials for inclusion in the SLR and NMA
- The comparators included within the network for each subgroup of interest
- The outcomes considered in NMA
- The statistical approach to NMA for each outcome; with the exception of the arm-based approach of the NMA, which may have resulted in biased relative treatment effects due to over-inflated posterior variances
- The additional analyses and sensitivity analyses conducted by the company in consideration of inconsistency and heterogeneity of treatment effect due to trial or participant characteristics; however, these analyses were conducted only within the ITT population, therefore it is unclear whether inconsistency or heterogeneity is presented in analyses of the HDA-RRMS, RES-RRMS and SOT-RRMS subgroups.
- The presentation of results from NMA models using random-effects for the ITT population due to anticipated heterogeneity between trials included in the network; however the ERG is uncertain whether important statistical inconsistency or heterogeneity is present within the results for the subgroups
- The company interpretations of the relative treatment effects from the NMA.

The ERG highlights the following points:

- Results of the NMAs undertaken for the efficacy outcomes of interest (qualifying ARR, 3 month CDP at 24 months and 6 month CDP at 24 months), generally show a numerical and/or statistically significant advantage for cladribine tablets compared to most comparators, aside from alemtuzumab and natalizumab, where NMA results generally showed a numerical disadvantage for cladribine tablets
- The company states that certain NMA results (such as the comparison of cladribine tablets against alemtuzumab) should be interpreted with caution due to difference in trial designs and participant characteristics of trials included in the network. The ERG considers that any heterogeneity present in the network will impact on all comparisons made within that network and therefore all NMA results should be interpreted with caution rather than just specific comparisons
- A major limitation of the NMAs performed by the company was the paucity of data available for the key efficacy outcomes; particularly for alemtuzumab to other in-scope therapies in the RES-RRMS and SOT-RRMS populations via a classic NMA approach. Therefore the company performed an additional meta-regression with the aim of estimating the efficacy of relevant DMTs compared to placebo in the RES-RRMS and SOT-RRMS, by relating efficacy to baseline risk, and centering baseline risk to the expected value in each group
- In principle, the ERG considers the company approach to the meta-regression generally appropriate with regards to the trials and comparators included within the meta-regression, the statistical methodology employed, the model selection criteria and choice of most appropriate model and the interpretation of meta-regression results
- The company concludes that the meta-regression predicted that all comparators are less effective in the SOT-RRMS subgroup than in RES-RRMS subgroup and, due to the significant overlap in the credible intervals across all comparisons, no therapy statistically dominates in terms of efficacy
- However, the ERG is not convinced by the validations of the meta-regression presented by the company, and whether the application of this meta-regression approach, outlined in by the NICE DSU in the context of considering baseline risk as a source of between-trial heterogeneity, is appropriate and valid for the objectives of the company. Therefore, the ERG encourages caution when interpreting the results of this meta-regression for the RES-RRMS and SOT-RRMS subgroups.

5 COST EFFECTIVENESS

5.1 Introduction

A summary of the evidence provided by the company in support of the use of cladribine tablets for the treatment of RRMS is provided in Sections 5.2 to 5.5 of this report. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature (see Section 5.2) and (ii) a report of the company's de novo economic evaluation, which included the development of a model using Microsoft Excel (see Section 5.3 and Section 5.4). A structured critique of the economic evidence submitted by the company is provided in Section 5.5

5.2 Objective of the company's cost effectiveness review

The company's systematic review was carried out to identify studies that considered the cost effectiveness of treatments for RRMS. The company searched five databases (on 30 January 2017). These, and the interface used for each search, are listed in Table 34.

Table 34 Details of the databases searched for economic evidence

Database	Interface
Excerpta Medica Database (Embase®)	Embase.com
Medical Literature Analysis and Retrieval System Online (MEDLINE®)	Embase.com
MEDLINE® In-Process	Pubmed.com
National Health Service Economic Evaluation Database (NHS EED)	Cochrane library
EconLit®	AEAweb.org interface

Source: CS, Appendix G

The company also carried out searches to identify conference abstracts published between 2012 and 2016 from the following congresses:

- International Society for Pharmacoeconomics and Outcomes Research (ISPOR): Annual International Meeting
- ISPOR: Annual European Congress
- ISPOR: Latin America Conferences
- Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS)
- European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS)
- American Academy of Neurology (AAN)
- American Neurological Society (ANA)
- European Federation of Neurological Societies (EFNS)
- European Neurological Society (ENS)
- Consortium of Multiple Sclerosis Centers (CMSC)
- Academy of Managed Care Pharmacy (AMCP).

In addition, hand searches of websites were performed to identify economic models submitted to HTA organisations. These searches were limited to appraisals reported after 2005.

5.2.1 Eligibility criteria used in study selection

The main inclusion criteria that were used to select studies are shown in Table 35. However, as the review was undertaken to identify information relevant to decision making in England, only peer-reviewed journal publications that reported cost effectiveness results in the UK were considered in detail.

Table 35 Economic review inclusion criteria

Characteristic	Inclusion criteria
Population	• Adults aged 18 and over
Interventions / comparators	• Cladribine tablets • IFN-ß 1a (Avonex, Rebif) • IFN-ß 1b(Betaferon, Betaseron) • Glatirmer acetate (Copaxone) • PEG-IFN- ß 1a (Plegridy) • Natalizumab (Tysabri) • Alemtuzumab (Lemtrada) • Fingolimod (Gilenya) • Dimethyl fumarate (Tecidera) • Teriflunomide (Aubagio) • BSC (author's definition) • Placebo • No treatment • Any other intervention
Outcomes	• All
Study design	• Cost-effectiveness analyses • Cost-utility analyses • Cost-benefit analyses • Cost-minimization analyses • Cost-consequence studies • Budget impact models
Country	• No restriction
Exclusion	• Cost studies, surveys, database analyses

BSC=best supportive care
Source: CS Appendix G, Table 32

5.2.2 Included and excluded studies

The searches identified eight studies[64-71] reporting the cost effectiveness of the use of DMT to treat people with RRMS in the UK and eight NICE TA appraisals.[15-20,72,73] None of the identified studies reported the cost effectiveness of cladribine tablets. Seven[64-66,68-71] of the eight studies reported incremental cost effectiveness ratios (ICERs) per QALY gained. Only two studies[68,69] reported results for the populations considered by the company (people with RES-RRMS[69] and SOT-RRMS[68]). Cost effectiveness results for people treated with natalizumab were

reported in one study[69] and results for people treated with fingolimod were reported in two studies.[68,69] None of the identified studies reported cost effectiveness results for people treated with daclizumab or alemtuzumab.

The 11 economic models submitted to NICE as part of the technology appraisals process included six submitted to the STA process and five submitted to an ongoing MTA:

- Natalizumab (TA127)[17]
- Fingolimod (TA254)[72]
- Teriflunomide (TA303)[73]
- Alemtuzumab (TA312)[19]
- Dimethyl Fumarate (TA320)[18]
- Daclizumab (TA441)[20]
- Beta-interferon and glatiramer acetate (ID809 [ongoing] - review of TA32).[15]

5.2.3 Findings from the cost effectiveness review

Of the eight published studies[64-71] relevant to the UK that were identified via the electronic database searches, only two[68,69] reported the cost effectiveness of DMT in RES-RRMS or SOT-RRMS. Maruszczak[68] reported the cost effectiveness of treatment with fingolimod versus DMF in patients with highly active RRMS (as defined in the SmPC[8] for fingolimod, and considered by the company to represent the SOT-RRMS cohort). Reported results suggest that, the ICER for the comparison of the cost effectiveness of treatment with fingolimod versus dimethyl fumarate is £14,076 per QALY gained. The company report (CS, Table 58) that results from Montgomery[69] suggest that the ICER for the comparison of the cost effectiveness of treatment with fingolimod versus natalizumab in patients with RES-RRMS is £15,313 per QALY gained (the ERG was unable to find this figure in the quoted source). Further findings from the review of identified studies may be found in Appendix G of the CS.

The company examined the documents related to previous NICE TAs[10,17-20,72,73] in detail and used decisions that had previously been made by NICE ACs to inform the design of their economic analyses. In particular, the company took note of the following points:

- Inclusion of the long-term waning in drug efficacy for all therapies, including cladribine, rather than assuming that efficacy persists indefinitely
- Use of health state utility values from the CLARITY study (rather than from published studies)
- Re-initiation of treatment with alemtuzumab (and of cladribine)
- Use of the EMA preferred endpoint of 6-month (rather than 3-month) CDP
- Natural history improvements and progression in EDSS modelled based on analyses of data from the British Columbia registry (rather than the London Ontario registry)

- A faster rate of progression in those with SOT-RRMS or RES-RRMS when compared to less active disease
- Consideration of non-medical costs.

The company's review of information from previously conducted TAs also highlights that the following assumptions and inputs have been accepted by NICE Appraisal Committees (ACs):

- The high level of uncertainty around treatment pathways and insufficient data to populate a model necessitate focusing assessment on only one line of treatment
- Consideration should be given to the impact of disability progression on the health utility of caregivers
- Benefits of an oral drug may not be fully captured by QALY estimates.

5.3 ERG critique of the company's literature review

The company reports full details of the searches used to identify cost effectiveness evidence in Appendix G of the CS. These searches included an appropriate cost effectiveness filter. The ERG highlights that search terms were not used consistently between databases. This approach is not considered good practice as it means that, across databases, the searches are inconsistent. In addition, the ERG notes that the searches were carried out in January 2017 and therefore some relevant studies may have been missed. The ERG updated the company searches for the period between January and July 2017 and is satisfied that no relevant studies have been missed.

The company also undertook two additional literature reviews, one focusing on HRQoL data and the other on costs and health care resources, to identify appropriate parameter values to use in their economic model. The ERG considers that undertaking such reviews is good practice and recognises the workload that was required. Full details of the company searches, and the accompanying reviews of evidence are reported in Appendix H and Appendix I of the CS.

5.3.1 NICE reference case checklist

Table 36 NICE Reference case checklist completed by ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Decision problem	The scope developed by NICE	Partial. Cost effectiveness results were only generated for two subgroups of the wider population specified in the final scope issued by NICE (RES-RRMS and SOT-RRMS)
Comparator(s)	As listed in the scope developed by NICE	Partial. Not all the comparators listed in the final scope issued by NICE were considered by the company. However, the comparators included in the company's cost effectiveness analyses were relevant to the RES-RRMS and SOT-RRMS subgroups
Perspective costs	NHS and PSS	Partial. The ERG considers the inclusion of informal care costs was inappropriate and outside of the NICE reference case
Perspective benefits	All direct health effects, whether for patients or, when relevant, carers	Partial. The ERG considers the inclusion of carer disutility was inappropriate and outside of the NICE Reference Case
Form of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on outcomes	Based on systematic review	Trial data as well as data from the company's NMAs and meta-regression were used to populate the company model
Outcome measure	Health effects should be expressed in QALYs.	Yes
Health states for QALY	Standardised and validated instrument. The EQ-5D is the preferred measure of health-related quality of life in adults	Yes – however, values from multiple sources were used to populate the model
Benefit valuation	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Yes
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Sensitivity analysis	Probabilistic sensitivity analysis	Yes

EQ-5D=EuroQol-5 dimension; QALY=quality adjusted life year; HRQoL=health-related quality of life; PSS=Personal Social Services

5.3.2 Model structure

Overview of the model

The company's model has been designed to assess the incremental cost effectiveness of treatment with cladribine tablets versus alternative treatments for people with RES-RRMS and SOT-RRMS. A natural history reference model (developed using the disability and relapse status data of people receiving BSC) has been enhanced by incorporating trial data that provided evidence for the comparative efficacy of DMTs versus placebo. The basic structure comprises 11 health states: 10 EDSS states and a single state for death from all causes (see Figure 3). At model entry, patients are assigned to each of the EDSS health states based on the proportions of patients recruited to the CLARITY trial who were, at baseline, in each state. In each cycle period (1 year) the cohort is at risk of moving to a higher EDSS state, moving to a lower EDSS state, remaining in the current EDSS state, or dying. In addition, during each cycle, patients are at risk of experiencing one or more acute relapse events or discontinuing treatment. Patients who discontinue DMT are assumed to receive BSC (although it is recognised that this is a simplification as some people are likely to receive further DMT treatment). Costs are calculated based on EDSS state, number of relapses and time in each state. Health effects are modelled in terms of QALYs, which take into account the effect of disability status, relapses and drug-related AEs.

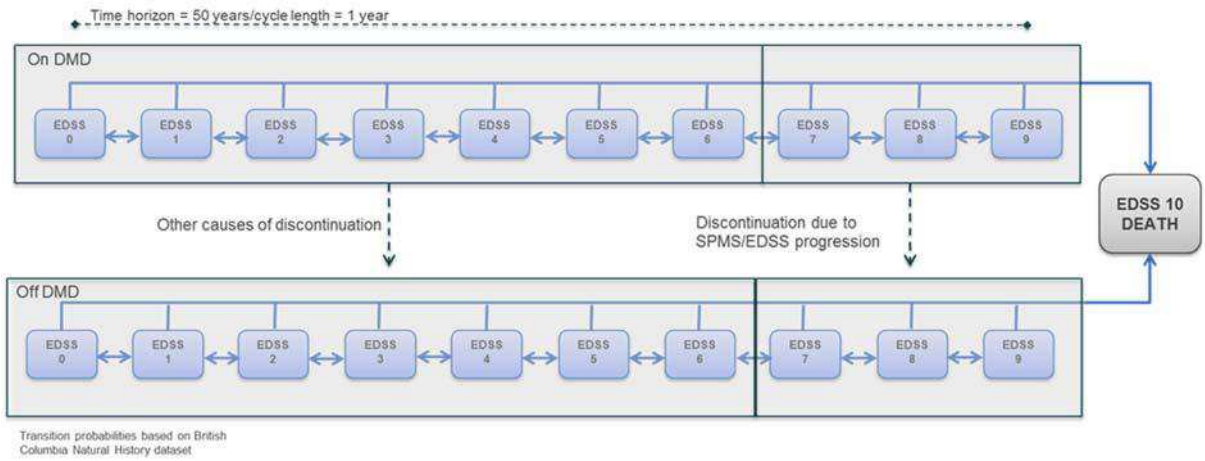

Figure 3 Health state structure of the company model

Source: CS, Figure 12

5.3.3 Population

Four subpopulations of people with RRMS are considered by the company. The company's analyses relate to people with RES-RRMS and SOT-RRMS, defined as follows:

- RES-RRMS: people with two or more relapses in the prior year, whether on treatment or not, and at least one T1 Gd+ lesion

- SOT-RRMS: people with one or more relapse in the prior year while on DMT, and at least one T1 Gd+ lesion or 9 T2 lesions.

These two populations are then subdivided, as shown in Table 37, depending on whether people are able to receive alemtuzumab.

Table 37 Modelled patient populations

Able to receive alemtuzumab	
Yes	**No**
RES-RRMSa	RES-RRMSb
SOT-RRMSa	SOT-RRMSb

Although people with active RRMS are included in the final scope issued by NICE, the company has not considered this population in any of their economic analyses as the anticipated EMA licence for cladribine was not expected to include this specific population.

Key baseline characteristics of the modelled populations, derived from the CLARITY trial, are provided in Table 38.

Table 38 Key model baseline population characteristics

Characteristic	**ITT (for reference)**	**RES-RRMS**	**SOT-RRMS**
Mean age (se)	38.7 years (0.474)	[redacted]	[redacted]
Female to male ratio:	1.933	[redacted]	[redacted]
Relapse in prior 12 months 0 1 2 >3	 0 (0.0%) 306 (70.0%) 110 (25.2%) 21 (4.8%)	[redacted]	[redacted]
Baseline EDSS			
EDSS 0	2.9%	[redacted]	[redacted]
EDSS 1.0	3.0%	[redacted]	[redacted]
EDSS 2.0	31.4%	[redacted]	[redacted]
EDSS 3.0	24.3%	[redacted]	[redacted]
EDSS 4.0	23.7%	[redacted]	[redacted]
EDSS 5.0	9.8%	[redacted]	[redacted]
EDSS 6.0	5.1%	[redacted]	[redacted]

EDSS=expanded disability status scale; ITT=intention-to-treat; se=standard error
Source: CS, Table 59 (Merck data on file)

5.3.4 Interventions and comparators

The company's economic evaluation compares the cost effectiveness of cladribine versus four of the comparators listed in the final scope issued by NICE (discussed in Section 3.6 of the ERG report). The methods used to deliver each of the DMTs considered in the company's analyses are summarised in Table 39. For each population considered in the company analyses, treatment with cladribine is compared with two comparator DMTs (see Table 40).

Table 39 Method of delivery of DMTs considered in the company's economic evaluation

DMT	Method of delivery
Cladribine tablets	Each treatment course consists of two treatment weeks, one at the beginning of the first month of year 1 and one at the beginning of the second month of year 2. Each treatment week consists of 4 or 5 days on which a patient receives one or two tablets (depending on body weight) as a single daily dose
Alemtuzumab	An infusion delivered on five consecutive days during week one of year one and on three consecutive days during week one of year 2
Daclizumab	A once monthly injection continued until treatment discontinuation
Fingolimod	One tablet a day until treatment discontinuation
Natalizumab	An infusion delivered once every 4 weeks until treatment discontinuation

DMT=disease modifying therapy

Table 40 Modelled comparators

Population	Comparator
RES-RRMSa	Natalizumab
	Alemtuzumab
RES-RRMSb	Natalizumab
	Daclizumab
SOT-RRMSa	Fingolimod
	Alemtuzumab
SOT-RRMSb	Fingolimod
	Daclizumab

Discontinuation

The company has assumed that any patient transitioning to EDSS state 7.0 or greater would have SPMS and, hence, would discontinue therapy. The company has explored the impact of varying the EDSS state 'cut-off' in a sensitivity analysis.

The modelling of treatment discontinuation due to reasons other than clinical diagnosis, for example, due to tolerability, has been captured through the implementation of a separate annual discontinuation probability. This is applied in each cycle and, in the base case, varies by treatment but is constant over time. The company has undertaken sensitivity analyses to explore the impact of varying the discontinuation probability over time.

Alemtuzumab and cladribine tablets are prescribed as two treatment courses administered over a 2-year period, with an interval of 12 months between the first and second course. Therefore, the concept of discontinuation is not relevant. The company has, however, applied the discontinuation probability to the first cycle to account for discontinuations between the first and second courses.

5.3.5 Perspective, time horizon and discounting

The company states that the economic evaluation was undertaken from the perspective of the NHS and PSS. The cycle length was one year, the time horizon was set at 50 years and, in line with the NICE Guide to the Methods of Technology Appraisal,[31] both costs and outcomes have been discounted at 3.5% per annum.

5.3.6 Treatment effectiveness and extrapolation in the base case

Natural history model - acute relapse events

Relapse rates are modelled as a function of time and have been estimated by multiplying the number of patients alive by the qualifying ARR derived from published sources (CS, p99). The qualifying ARR in the first year is modelled using rate data from the placebo arm of the CLARITY trial (RES-RRMS: mean=[redacted], SOT-RRMS: mean=[redacted]). In the base case, the qualifying ARR in subsequent years relies on adjusting the first-year value using data from the British Columbia Multiple Sclerosis (BCMS) registry.[6]

Natural history model - duration of relapse events

Relapses have been divided into two categories depending on whether hospitalisation was required. Pooled ITT data from the CLARITY trial have been used to estimate duration of events (see Table 41). These estimates have been applied to relapses experienced on all treatments considered in the analyses.

Table 41 Length of relapse events

Relapse event	Mean (sd)
Duration of relapses requiring hospitalisation	34.41 days (6.38 days)
Duration of relapses not requiring hospitalisation	38.64 days (6.20 days

sd=standard deviation
Source: CS, Table 64

Natural history model – EDSS progression

Transition matrices for the natural history of RRMS were identified from previous NICE appraisals[18,19,72,73] and publications associated with the UK risk-sharing scheme.[74,75] The matrix with on a median age of onset of over 28 years was used in the base case, in keeping with the mean baseline age (38.7 years) and disease duration (5.18 years) of the modelled population (Table 42).

Table 42 Annual base case EDSS transition probabilities (multiple sclerosis age of onset ≥28 years)

State (from \to)	0	1–1.5	2–2.5	3–3.5	4–4.5	5–5.5	6–6.5	7–7.5	8–8.5	9–9.5
0	0.69537	0.20294	0.07251	0.02170	0.00422	0.00137	0.00175	0.00011	0.00003	0.00000
1–1.5	0.05826	0.69501	0.15783	0.06088	0.01638	0.00458	0.00643	0.00048	0.00013	0.00001
2–2.5	0.01586	0.12133	0.60789	0.16796	0.04458	0.01849	0.02159	0.00174	0.00052	0.00004
3–3.5	0.00594	0.04960	0.12006	0.54422	0.09109	0.05845	0.11649	0.01030	0.00355	0.00030
4–4.5	0.00165	0.2214	0.06660	0.11519	0.48935	0.10388	0.16811	0.02580	0.00671	0.00056
5–5.5	0.00052	0.00533	0.02942	0.05866	0.08736	0.48695	0.27310	0.03880	0.01883	0.00102
6–6.5	0.00012	0.00133	0.00444	0.02497	0.03069	0.04080	0.74069	0.10897	0.04377	0.00423
7–7.5	0.00001	0.00015	0.00052	0.00247	0.00727	0.00385	0.11684	0.69269	0.16061	0.01559
8–8.5	0.00000	0.00001	0.00004	0.00029	0.00055	0.00050	0.01881	0.05574	0.90340	0.02066
9–9.5	0.00000	0.00000	0.00000	0.00002	0.00004	0.00003	0.00176	0.00568	0.17414	0.81832

Source: CS, Table 66 (Palace 2014[74])

Natural history model – progression rate adjustments

Progression rates in the natural history model have been adjusted for patients with RES-RRMS and SOT-RRMS. To account for faster progression, the model includes an acceleration parameter that is used to increase the probability of EDSS progression prior to the adjustment for the effect of DMT (see Table 43). The adjustment is applied to the probability of progression associated with each EDSS state. Based on advice from the company's clinical experts, the adjustment is applied to EDSS states 0 to 6 as progression rates are expected to return to baseline levels once patients develop SPMS (i.e. transition to EDSS 7.0 or greater). The adjustment was estimated using data from the CLARITY trial.

Table 43 Hazard rate adjustments

Group	Hazard rate adjustment EDSS 0 to 6	Note
RES-RRMS	[redacted]	Calculated by comparing progress by week 96 in RES-RRMS population versus progress in non-RES-RRMS population (placebo arm) in the placebo arm of the CLARITY trial
SOT-RRMS	[redacted]	Progression rates were lower in the placebo SOT-RRMS group than the placebo active RRMS population. This was considered not to be plausible and, therefore, the hazard rate adjustment was assumed to equal the ratio of the annualised relapse rates of the placebo group SOT-RRMS population versus the placebo group active population

EDSS=expanded disability status scale
Source: CS, Table 68

Natural history model – mortality risk

Transitions to the death state have been assumed to be independent of EDSS state. The annual probability of death was estimated by inflating Office for National Statistics (ONS) gender-averaged all-cause mortality rate by published excess mortality risk rates comparing

mortality in the population with RRMS versus the general population.[76] Next, the inflated mortality rates were converted into annual (cycle) probabilities.

Treatment adjusted model – relapse rate

The relapse rate ratios have mainly been obtained from the company's NMA (FE model), although the efficacy of alemtuzumab and daclizumab for the SOT-RRMS subgroup had to be assumed due to lack of available data. A summary of the ratios used in the model is provided in Table 44.

Table 44 Ratio of annualised relapse rates comparing DMT versus placebo

Treatment versus placebo	Median ratio of annualised relapse rates comparing treatment versus placebo [upper 95% crl to lower 95% crl value]	
	RES-RRMS	SOT-RRMS
Cladribine	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]
Fingolimod	Not in scope	[redacted]
Natalizumab	[redacted]	Not in scope
Daclizumab	[redacted]	[redacted]

*based on relapse rate ratio from CARE MS-II study
**assumed to have the same effect as cladribine
Crl=credible interval; DMT=disease modifying therapy
Source: CS, Table 69

Treatment adjusted model – EDSS progression

The effect of DMT on progression between EDSS states was modelled using data on confirmed disability at 6 months. A meta-regression analysis was used to generate hazard ratios between each DMT and placebo. The log-hazard ratios used in the model (see Table 45) correspond to the effect of DMT versus placebo for patients with a baseline probability of progression that is equal to the mean progression probability in the RES-RRMS population of CLARITY.

Table 45 Normalised progression hazard ratios

DMT	Normalised hazard ratio*	
	RES-RRMS	SOT-RRMS
Cladribine	[redacted]	[redacted]
Alemtuzumab	[redacted]	[redacted]
Daclizumab	[redacted]	[redacted]
Fingolimod	Not applicable	[redacted]
Natalizumab	[redacted]	Not applicable
Population risk	[redacted]	[redacted]

DMT=disease modifying therapy
*Derived from log-hazard ratio and baseline risk
Source: CS, Table70

The company highlights that the results of their meta-regression analysis show significant overlap in the credible intervals for the hazard ratios of confirmed disability progression at 6 months for both subgroups, and that no therapy statistically dominates in terms of this outcome measure.

Treatment adjusted model – waning of drug efficacy

The long-term treatment effects of the intervention and comparators are unknown. The company has assumed that the effect of treatment will decrease over time (known as waning). This assumption has been modelled by adjusting the hazard ratio for drug effect. The annual proportions of drug effect for alemtuzumab, daclizumab, fingolimod and natalizumab are displayed in Table 46.

The company's assumptions relating to the waning effect of treatment with cladribine tablets are based on a post-hoc analysis of data collected during the CLARITY and CLARITY-EXT trials that explored whether the treatment effect observed during the CLARITY trial persists in the absence of additional treatment. The rank preserving structural failure time model (RPSFTM) and the iterative parameter estimation (IPE) algorithm have been used to estimate the effect of patients switching from placebo to intervention in the placebo/intervention group of the CLARITY-EXT trial.

Results from the company's analyses suggest that the effect of treatment with cladribine tablets was approximately constant over the 4 years for which data are available. However, the effectiveness beyond 4 years remains uncertain.

Table 46 Changes in drug effect over time

Years	Proportion of DMT effect	
	Cladribine	Alemtuzumab, daclizumab, fingolimod and natalizumab
0 to 2	100%	100%
2 to 4	100%	75%
4 to 5	75%	75%
5+	50%	50%

DMT=disease modifying therapy
Source: CS, Table 71 and Table 73

Treatment adjusted model – safety and tolerability

The company's probability estimates of experiencing drug-related AEs or tolerability issues are based on clinical trial data identified in the systematic literature review. Values used in the model are presented in Table 47.

Table 47 Absolute probabilities of adverse events by DMT and event type

Event type	Cladribine	Alemtuzumab	Natalizumab	Fingolimod	Daclizumab
Recurring events that apply to each year treated in the model					
Infusion site reaction	0%	90.1%	23.6%	0%	0%
Injection site reaction	0%	0%	0%	0%	2.0%
One-off events that apply at the start of the model time horizon					
PML	0%	0%	0.213%	0.001%	0%
Macular oedema	0%	0%	0%	0.394%	0%
Malignancy	0.60%	0.60%	0.60%	0.60%	0.60%
Hypersensitivity reaction	0%	0%	4.0%	0%	0%
Gastrointestinal disorder	24.5%	22.8%	22.8%	30.4%	22.8%
Thyroid related events	5.1%	11.3%	1.2%	1.2%	1.2%
Immune thrombocytopenic purpura	0%	1.8%	0%	0%	0%
Serious infection	2.8%	2.3%	1.9%	2.2%	10.1%
Influenza like illness	1.3%	1.1%	0.1%	0.5%	1.5%

PML=progressive multifocal leukoencephalopathy; DMT=disease modifying therapy
Source: CS, Table 74

Treatment adjusted model – discontinuation

The probability of treatment discontinuation has been estimated from reported all-cause discontinuation rates that occurred in the trials that are included in the company's 6-month CDP NMA. Fifteen of the 18 studies included in this NMA reported discontinuation data. The reported discontinuation probabilities have been converted to annualised probabilities and, for each DMT, a weighted mean probability was calculated based on the number of patients in each study. The probabilities used in the company model are presented in Table 48.

Table 48 Discontinuation probabilities used in the company model

DMT	Data sources (trials)	Discontinuation probability
Cladribine	CLARITY	4.854%
Alemtuzumab	CAMMS223, CARE-MS I, CARE-MS II	2.266%
Daclizumab	Decide	11.609%
Fingolimod	FREEDOMS, FREEDOMS II	13.595%
Natalizumab	AFFIRM	6.4%

DMT=disease modifying therapy
Source: CS, Table75

5.3.7 Health-related quality of life

As part of CLARITY and CLARITY-EXT trials, EQ-5D-3L questionnaires were administered on day 1, week 24, week 48, week 72, at the week 96/early termination visit, and at each relapse evaluation. Data from completed questionnaires were mapped to the health state utility

(HSU) index values using the UK social tariff. The company also carried out a systematic literature review to identify relevant HRQoL data.

Following an assessment of available evidence the company used data from the CLARITY trial to represent the HRQoL of people in EDSS 0 to 5, data from Hawton[24] for EDSS 6.0 to 8.0, and data from Orme[77] for EDSS 9.0. The company reports that this approach is in line with the approach taken in previously submitted company models.[17-20,72,73]

Table 49 Mean health state utility values used in the company model

Health state	CLARITY	Hawton[24]	Orme[77]
Age	38.3 years	50.7 years	51.4 years
EDSS 0	[redacted]	0.846 (0.026)	0.87 (0.045)
EDSS 1.0	[redacted]	0.762 (0.025)	0.799 (0.093)
EDSS 2.0	[redacted]	0.711 (0.019)	0.705 (0.093)
EDSS 3.0	[redacted]	0.608 (0.029)	0.574 (0.097)
EDSS 4.0	[redacted]	0.609 (0.028)	0.61 (0.093)
EDSS 5.0	[redacted]	0.531 (0.031)	0.518 (0.092)
EDSS 6.0	Not available	0.496 (0.012)	0.46 (0.093)
EDSS 7.0	Not available	0.392 (0.032)	0.297 (0.094)
EDSS 8.0	Not available	0.025 (0.038)	-0.049 (0.109)
EDSS 9.0	Not available	Not available	-0.195 (0.119)

EDSS=expanded disability status scale
Source: CS, Table 77

Impact of relapses on health state utility

Following their review of HRQoL literature, the company identified Ruutiainen[78] and Orme[77] to be their preferred sources of parameter values for the effect of relapses on HRQoL as the values in these papers had been generated by regression analyses that adjusted for EDSS staging. However, the same value was used for hospitalised and non-hospitalised events, as hospitalisation status was not reported in either paper. The values used in the model are presented in Table 50.

Table 50 Impact of relapse events on health state utility

Health state	Duration (days)	Orme[77]	Ruutiainen[78]
Relapse requiring hospitalisation	34.41	-0.071	-0.066
Relapse not requiring hospitalisation	38.64		

Source: CS, Table 80

Impact of adverse events on health state utility

The company's search for HRQoL literature did not identify any studies reporting the impact of treatment related AEs on health state utility. The company, therefore, carried out additional ad hoc searches to identify relevant data from previous appraisals of therapies for the treatment of RRMS and other chronic conditions. The company combined disutility estimates

with duration of event estimates to generate an estimate of QALY impact. The values used by the company have been taken from Boye,[79] NICE Technology Appraisal Guidance (TA312)[19] and Trogdon.[80]

Table 51 Adverse event disutilities

Adverse event	Duration (days)	Disutility
Infusion site reaction (alemtuzumab and natalizumab)	5	-0.011
Injection site reaction (monthly)	13	-0.011
PML	93.1	-0.200
Severe infection	14	-0.190
Macular oedema	84	-0.040
Gastrointestinal	8	-0.240
Hypersensitivity	7	-1.000
Autoimmune thyroid-related event	365.25	-0.110
Influenza-like symptoms	7	-0.210
Malignancy	365.25	-0.116
Immune thrombocytopenic purpura	28	-0.090

PML=progressive multifocal leukoencephalopathy; QALY=quality adjusted life year
Source: CS, Table 81

5.3.8 DMT related resource use and costs

Drug costs comprise three different components: acquisition, administration and monitoring. The costs of treatment with daclizumab, fingolimod and natalizumab are based on the number of people on therapy in each EDSS. All patients are assumed to adhere to therapy and take their full course in each cycle.

The costs of treatment with alemtuzumab and cladribine tablets are based on the proportion of patients eligible for therapy (EDSS<7) at the start of each cycle multiplied by the proportion treated. Given the uncertainty around long-term rates of relapse, re-initiation of treatment was only modelled up to year 6.

Model values for the proportions of patients treated with cladribine tablets have been based on time to first relapse in the intervention/placebo arm of the CLARITY and CLARITY-EXT trials. The estimates for re-treating patients with alemtuzumab are those used in TA441.[20] Proportions of patients eligible for treatment with cladribine tablets and alemtuzumab are provided in Table 52. Reasons for not completing a course of treatment include disease progression, and intolerance. Adjustments for these influences are accounted for separately within the model.

Table 52 Proportions of patients eligible for treatment with cladribine and alemtuzumab

Years	Proportion of eligible patients treated	
	Cladribine	Alemtuzumab
1	100%	100%
2	100%	100%
3	[redacted]	28%
4	[redacted]	11%
5	[redacted]	1%
6	[redacted]	0%

Source: CS, Table 84

Drug acquisition costs

Drug acquisition costs have been estimated using list prices for medications (British National Formulary [BNF][81]) and also for the model estimate of the mean total dose of therapy administered during each cycle. A summary of the total acquisition costs of each therapy considered in this appraisal is provided in Table 53. The company has varied the cost of cladribine tablets between the RES-RRMS and SOT-RRMS patients due to small differences in the weight distributions of the two cohorts in the CLARITY trial.

Table 53 Total drug acquisition costs (list prices)

Therapy	Pack size	Pack cost	Dose	Units per year year 1 / year 2+	Total annual cost	
					Year 1	Year 2+
Cladribine: RES-RRMS patients	1 x 10mg tab	£2,047	0.875mg/kg per dose	2 / 2	£25,917	£25,917
Cladribine: SOT-RRMS patients	1 x 10mg tab	£2,047	0.875mg/kg per dose	2 / 2	£26,373	£26,373
Alemtuzumab	12mg vial	£7,045	12mg per infusion	5 / 3	£35,225	£21,135
Daclizumab	1-syringe	£1,597	Once monthly	12.0	£19,160	
Fingolimod	28-cap	£1,470	1 tab per day	365.25	£19,176	
Natalizumab	15ml-vial	£1,130	Once every 4 weeks (300mgs equating to 1x 15ml-vial)	13.0	£14,690	

Source: CS, Table 85

Drug administration

Drug administration costs include the cost of admissions for infusions, additional medications provided alongside therapy, and any additional district nurse or neurologist visits required for the support of drug administration. The unit costs of drug administration are presented in Table 54.

Table 54 DMT administration costs

Therapy	Delivery method	Source	Administration resources consumed per year	Total cost	
				Year 1	Year 2+
Cladribine	Oral	Draft SmPC[28]	No administration requirements	£0	£0
Alemtuzumab	Infusion	TA312 CS[19]	5 x admissions in year 1 plus 3 x 1g vials of methylprednisolone, 1 pack of paracetamol and two packs of aciclovir (200mg) 3 x admissions in subsequent years plus 3 1g vials of methylprednisolone, 1 pack of paracetamol and two packs of aciclovir (200mg)	£2,782	£1,681
Fingolimod	Oral	TA312 CS[19]	Admission during first year to monitor ECG	£551	£0
Natalizumab	Infusion	SmPC[7]	Monthly admissions for infusions (13 in total)	£7,159	£7,159
Daclizumab	Subcutaneous	Assumption in line with that used in previous appraisals	Training for self-administration of device	£204	£0

CS=company submission; ECG=electrocardiogram; SmPC=summary of product characteristics
Source: CS, Table 86

Monitoring of patients receiving DMTs

The annual costs, first and subsequent years, of monitoring patients taking DMTs are provided in Table 55 and Table 56 respectively. The costs have been assumed to vary between first and subsequent years to take into account the increased testing that typically occurs when therapies are initiated. However, for patients receiving natalizumab, the costs remain high as receipt of this therapy is associated with a high risk of progressive multifocal leukoencephalopathy (PML) and, therefore, ongoing MRI monitoring is required.

Table 55 Year 1 costs of monitoring patients receiving DMTs

Therapy	Source	Administration resources consumed in first year	Total cost Year 1
Cladribine	Draft SmPC[28]	1 x MRI scan 3 x complete blood counts 2x neurology visits 1x tuberculin skin test 1x HBV test 1xHCV test	£584
Alemtuzumab	SmPC[82] TA312 CS[19]	12 x complete blood counts 12 x biochemistry tests for serum creatinine levels 12 x urinalysis tests with microscopy 4 x thyroid function test (thyroid stimulating hormone level) 1 x tuberculin skin test 0.65 x human papilloma virus test (females only – assumption 65%) 2x neurology visits	£444
Daclizumab	TA441 CS[20]	13 x biochemistry tests 4 x complete blood count 2 x neurology visit	£349
Fingolimod	SmPC[8] TA312 CS[19]	1 x MRI scan 4 x complete blood count 6 x biochemistry tests (month 0,1,3, 6,9 and 12) 1 x ophthalmology assessment 3 x neurology visits	£821
Natalizumab	McGuigan 2016[83] TA312 CS[19]	1 x JC virus test 2 x biochemistry test 1 x MRI scan 2 x neurologist visit	£540

MRI=magnetic resonance imaging; JC virus=John Cunningham virus; SmPC=summary of product characteristics
Source: CS, Table 87

Table 56 Costs of monitoring patients receiving DMTs during year 2+

Therapy	Source	Administration resources consumed in subsequent year	Total cost Year 2+
Cladribine	Draft SmPC[28]	3 x complete blood counts 1 x neurology visits 1 x HBV test 1 x HCV test	£215
Alemtuzumab	SmPC[82] TA312 CS[19]	12 x complete blood counts 12 x biochemistry tests for serum creatinine levels 12 x urinalysis tests with microscopy 4 x thyroid function test (thyroid stimulating hormone level) 0.65 x human papilloma virus test (females only – assumption 65%) 1 x neurology visits	£267
Daclizumab	TA441 CS[19]	12 x biochemistry tests 4 x complete blood count 1 x neurology visit	£187
Fingolimod	TA312 CS[19] SmPC[8]	2 x complete blood count 2 x biochemistry test 1 x neurology visits	£169
Natalizumab	McGuigan 2016[83] [redacted]TA312 CS[17]	2 x JC virus test (six monthly) 2 x biochemistry test 1 x MRI scan 2 x neurology visits	£547

HBV=hepatitis B virus; HCV=hepatitis C virus; MRI=magnetic resonance imaging; JC virus=John Cunningham virus; SmPC=summary of product characteristics
Source: CS, Table 87

5.3.9 EDSS related resource use and unit costs

The company carried out a systematic review to identify published costs. The review included published peer reviewed costing studies, costing data used in models submitted to NICE as part of other STAs and the company's own unpublished data.

Direct medical costs

A summary of the direct medical costs used in the company's base case analysis is provided in Table 57. These costs are those reported by Hawton[24] (n=289). The cost year for the costs is 2012. The total costs include the costs of contact with a chiropodist, clinical psychologist, continence advisor, district nurse, dietician, GP, MS specialist nurse, neurologist, occupational therapist, ophthalmologist, physiotherapist, rehabilitation doctor, social worker, speech therapist, pain management service and/or rehabilitation/respite care. The costs reported by Hawton[24] only cover a 6-month period and, therefore, the company multiplied these by two to generate an annual (model cycle) rate. In addition, the company inflated the Hawton[24] costs to 2015/2016 prices using the hospital and community health services index.[84]

Table 57 Annual direct medical costs

State	Annual mean cost (sd) *
EDSS 0	£1,020 (281)
EDSS 1.0	£910 (168)
EDSS 2.0	£716 (92)
EDSS 3.0	£668 (81)
EDSS 4.0	£1,002 (110)
EDSS 5.0	£1,006 (120)
EDSS 6.0	£1,304 (94)
EDSS 7.0	£1,316 (180)
EDSS 8.0	£3,320 (395)
EDSS 9.0	Not reported

EDSS=expanded disability status scale; sd=standard deviation
*Costs are reported for a 6-month period and so have been multiplied by 2 to provide annual costs
Source: CS, Table 88

Direct non-medical costs

The company highlights that there is uncertainty around the extent to which non-medical costs can be considered to fall under the headings of an NHS and PSS perspective. The company, therefore, adopted the approach used in the CS for TA441,[20] namely that 80% of social and community care costs, and 47% of investment costs, should be considered in the analysis.

The company identified two studies that reported non-medical costs (Karampama[85] and Tyas[86]). The company uses the costs reported by Karampama[85] (inflated to 2015/2016 prices using the hospital and community care index[84]) in their model. These costs were used as insufficient detail was supplied by Tyas[86] to allow the costs reported in that paper to be adjusted so as to only include components relevant to an NHS and PSS perspective. A summary of the direct non-medical costs used in the company model is provided in Table 58.

Table 58 Annual non-medical direct costs used in the company model

	Unadjusted costs		Adjusted and inflated costs
	Investment	Professional and informal care	Total direct non-medical
Proportion of cost considered relevant to an NHS and PSS perspective	47%	80%	-
EDSS: 0 to 3.0	£23	£1,492	£1,675
EDSS: 4.0 to 6.5	£693	£7,074	£8,569
EDSS: 7.0 to 9.0	£1,405	£30,603	£35,592

EDSS=Expanded Disability Status Scale
Source: CS, Table 90

Costs of relapses

The company used costs reported by Hawton[24] (rather than those reported by Karampama[85]) in their base case analysis as these data are in line with the data they have chosen to use to model costs by EDSS state in the model. The costs associated with hospitalised and non-hospitalised relapse events have been estimated by subtracting the costs for those who had a relapse from the costs for those without relapse. Resultant costs have been inflated to 2015/2016 cost year using the hospital and community health services index.[84] The costs of relapse used in the company model are provided in Table 59.

Table 59 Cost of relapse events

Relapse state	Inflated cost per event
Relapse without hospitalisation	£526
Relapse with hospitalisation	£3,463

Source: CS, Table 92

5.3.10 Adverse events

The company has estimated resource use associated with AEs based on assumptions and information from published studies. Associated costs have been taken from the BNF,[81] NHS Reference Costs (2016)[87] and Unit Costs of Health and Social Care (2016).[84] The costs used in the company model are provided in Table 60.

Table 60 Adverse event costs

Adverse event	Cost
Infusion site reaction	£0
Injection site reaction	£6.79
PML	£1,268.11
Severe infection	£3,287.62
Macular oedema	£245.46
Gastrointestinal	£707.28
Hypersensitivity	£156.68
Autoimmune thyroid-related event	£543.63
Influenza-like symptoms	£6.79
Malignancy	£11,427.59
Immune thrombocytopenic purpura	£939.54

PML=progressive multifocal leukoencephalopathy
Source: CS, Table 93

5.3.11 Cost effectiveness results

Results from all the company's analyses show that treatment with cladribine tablets is cheaper than any of the comparators and generates more QALYs (see Table 61, Table 62, Table 63, and Table 64). However, as the company has used the list prices for daclizumab and fingolimod, the results from analyses involving these comparators are not relevant to the NICE AC's decision. Results generated by the company model using the PAS prices for daclizumab

and fingolimod and the company's base case assumptions, have been generated by the ERG and are included in the confidential appendix that accompanies this ERG report. In addition, cost effectiveness results, using PAS prices and following the ERG's amendments to the company model, are also included in this confidential appendix.

Table 61 Base case results for RES-RRMSa (list prices)

Technologies	Total			Incremental			ICER per QALY gained
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Cladribine	£480,441	22.176	8.098				
Alemtuzumab	£499,575	22.176	7.916	-£19,134	0.000	0.182	Cladribine dominant
Natalizumab	£611,117	22.176	7.586	-£130,676	0.000	0.512	Cladribine dominant

ICER=incremental cost effectiveness ratio; LYs=life years; QALYs=quality adjusted life years
Source: CS, Table 97

Table 62 Base case results for RES-RRMSb (list prices)

Technologies	Total			Incremental			ICER per QALY gained
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Cladribine	£480,441	22.176	8.098				
Daclizumab	£569,623	22.176	7.174	-£89,182	0.000	0.924	Cladribine dominant
Natalizumab	£611,117	22.176	7.586	-£130,676	0.000	0.512	Cladribine dominant

ICER=incremental cost effectiveness ratio; LYs=life years; QALYs=quality adjusted life years
Source: CS, Table 98

Table 63 Base case results for SOT-RRMSa (list prices)

Technologies	Total			Incremental			ICER per QALY gained
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Cladribine	£467,361	21.318	7.570				
Alemtuzumab	£484,910	21.318	7.417	-£17,549	0.000	0.153	Cladribine dominant
Fingolimod	£539,427	21.318	6.626	-£72,066	0.000	0.944	Cladribine dominant

ICER=incremental cost effectiveness ratio; LYs=life years; QALYs=quality adjusted life years
Source: CS, Table 99

Table 64 Base case results for SOT-RRMSb (list prices)

Technologies	Total			Incremental			ICER per QALY gained
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Cladribine	£467,361	21.318	7.570				
Daclizumab	£533,758	21.318	7.022	-£66,397	0.000	0.548	Cladribine dominant
Fingolimod	£539,427	21.318	6.626	-£72,066	0.000	0.944	Cladribine dominant

ICER=incremental cost effectiveness ratio; LYs=life years; QALYs=quality adjusted life years
Source: CS, Table 100

5.3.12 Sensitivity analyses

Deterministic univariate sensitivity analyses

The company carried out a wide range of univariate sensitivity analyses to show the impact of variation in parameters on the incremental net health effects. Each parameter was varied between its lower and upper 95% confidence, or credible, interval value, or by 50% of its mean value, if statistical measures of variance were not available. Tornado diagrams are presented in the CS (CS, Figure 23 to Figure 26). Results show that the base case analyses are most sensitive to variation in the effect of DMT on 6-month CDP. Other key drivers include the rate at which costs and outcomes are discounted, baseline risk, the adjustment factor applied to the natural history model to account for the faster EDSS progression of patients with RES-RRMS and treatment discontinuation.

Probabilistic sensitivity analysis

The company undertook probabilistic sensitivity analyses (PSAs) to assess the uncertainty surrounding the parameter values used in the model. Results from these analyses are displayed in Table 65 to Table 68. The results support the base case results as, for each analysis, the company shows that treatment with cladribine dominates all other treatments.

Table 65 Probabilistic results for RES-RRMSa (list prices)

Technologies	Mean costs	Incremental		ICER per QALY gained	Probability cost effective at £30,000 per QALY gained
		Costs	QALYs		
Cladribine	£475,162				63.7%
Alemtuzumab	£495,655	-£20,492	0.202	Cladribine dominant	36.3%
Natalizumab	£604,411	-£129,249	0.491	Cladribine dominant	0.0%

ICER=incremental cost effectiveness ratio; LYs=life years; QALYs=quality adjusted life years
Source: CS, Table 101

Table 66 Probabilistic results for RES-RRMSb (list prices)

Technologies	Mean costs	Incremental		ICER per QALY gained	Probability cost effective at £30,000 per QALY gained
		Costs	QALYs		
Cladribine	£471,594				96.9%
Daclizumab	£559,064	-£87,470	0.920	Cladribine dominant	2.6%
Natalizumab	£600,923	-£129,328	0.498	Cladribine dominant	0.5%

ICER=incremental cost effectiveness ratio; LYs=life years; QALYs=quality adjusted life years
Source: CS, Table 102

Table 67 Probabilistic results for SOT-RRMSa (list prices)

Technologies	Mean costs	Incremental		ICER per QALY gained	Probability cost effective at £30,000 per QALY gained
		Costs	QALYs		
Cladribine	£472,273				60.8%
Alemtuzumab	£491,914	-£19,641	0.198	Cladribine dominant	35.7%
Fingolimod	£538,566	-£66,293	0.873	Cladribine dominant	3.1%

ICER=incremental cost effectiveness ratio; LYs=life years; QALYs=quality adjusted life years
Source: CS, Table 103

Table 68 Probabilistic results for SOT-RRMSb (list prices)

Technologies	Mean costs	Incremental		ICER per QALY gained	Probability cost effective at £30,000 per QALY gained
		Costs	QALYs		
Cladribine	£472,012				84.5%
Daclizumab	£534,318	-£62,306	0.489	Cladribine dominant	11.9%
Fingolimod	£538,296	-£66,283	0.845	Cladribine dominant	3.6%

ICER=incremental cost effectiveness ratio; LYs=life years; QALYs=quality adjusted life years
Source: CS, Table 104

5.3.13 Scenario analyses

The company carried out scenario analyses to test the robustness of the model to variations in model assumptions and the use of alternative input parameters (including different utility values and different transition matrices for the natural history of disease). Analyses also considered use of societal perspective, alternative time horizons, assumptions on the durability of drug effect, and using a 21 health-state model.

5.3.14 In all of the scenarios except one, treatment with cladribine tablets was shown to dominate all other treatments. The exception was a scenario in which the cost effectiveness of treatment with cladribine tablets was compared with alemtuzumab in the population with RES-RRMS. In this scenario, results from a conventional NMA that used a different network to that used in the base case meta-regression analysis, were used in the model. Results showed that treatment with cladribine tablets was costed more (+£36,519) and was less effective (-1.071) than treatment with alemtuzumab. However, the company highlights that results from the NMA show that there was significant overlap in the 95% credible intervals for 6-month CDP and hence neither DMT was shown to be statistically superior to the other. Model validation and face validity check

The company employed a number of approaches to validate their economic model, including asking clinical experts and external health economists to check the face validity of the structure, assumptions and data used to populate the model. In addition, an external meta-analysis expert checked the meta-analysis regression model. Internal validity was tested through application of extreme value testing and by examination of model calculations by an independent modeller. Where possible, results were compared with published studies[63,88] and analyses of British Columbia registry data (CS, Figure 15).

5.3.15 Drummond checklist

Table 69 Critical appraisal checklist for the economic analysis completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Partially	No. Effectiveness data from the CLARITY trial were used to demonstrate the effectiveness of treatment with cladribine tablets versus placebo. The two outcomes used in the model are qualifying ARR and 6-month CDP. The results show the following: • **RES-RRMS** subgroup: treatment with cladribine tablets is not statistically significantly superior to placebo in terms of 6-month CDP but is statistically significantly superior in terms of qualifying ARR • **SOT-RRMS** subgroup: treatment with cladribine tablets is not statistically significantly superior to placebo in terms of either 6-month CDP or qualifying ARR Comparative effectiveness of treatment with cladribine tablets versus other DMTs was derived from the company's NMAs and meta-regression. The ERG has concerns about the reliability of results from these analyses

Were all the important and relevant costs and consequences for each alternative identified?	Yes	Partial. The ERG considers the inclusion of cost of informal care and carer disutility were inappropriate as both are outside of the NICE reference case
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Yes	
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	Yes	No. The company did not fully explain the limitations of the available clinical evidence

ARR=annualised relapse rate; CDP=confirmed disability progression; DMT=disease modifying therapy; ERG=evidence review group; NMA=network meta-analysis; RES=rapidly evolving severe; RRMS=relapsing-remitting multiple sclerosis; SOT=sub-optimal therapy

5.4 Detailed critique of the company's economic model

The company submitted a cost effectiveness model built in MS Excel. This model is a simplified version of economic models that, since 2005, have formed part of company submissions for NICE STAs of drugs for treating MS. Previously submitted models had a 21-health state structure: 10 states were based on EDSS state for patients with RRMS and a further 10 states were for patients with SPMS, with one additional state for death from all causes. The submitted company model comprises 11 health states: 10 EDSS based states and one additional state for death from all causes. The company's justification for employing a simplified 11 health-state model is that:

- HRQoL is more closely related to EDSS state than to the clinical form of MS
- It is difficult to identify the transition from RRMS into the SPMS subtype, making it challenging to reliably model the conversion from one form to the other
- The use of SPMS-specific health states requires the use of SPMS-specific transition rates. The only source of these data is the London Ontario registry and the company considered that these data were too limited to accurately estimate SPMS-specific transition rates.

The ERG is satisfied with the company's rationale for using the simplified 11 health-state model rather than a 21 health-state model. Clinical advice to the ERG is that SPMS subtype does not significantly impact on costs or HRQoL. Whilst EDSS state transition probabilities for the SPMS subtype would differ from those for the RRMS subtype, the ERG considers that any incorporation of this detail into the model is limited by available data on transition to the SPMS subtype and is satisfied that the 11 state simplification does not unduly influence model results.

Whilst an 11 health-state model is, by design, less complicated then a 21 health-state model, the algorithms required to build the model are extensive and have made it impossible for the ERG to fully check that they had all been correctly implemented. The Excel model frequently crashed when undertaking standard formula checking processes (e.g., checking the precedents and dependents of values in cells). The checks that the ERG was able to perform suggest that the model results are generated by accurate algorithms; however, the ERG is unable to guarantee that this is true for all the algorithms in the company model.

5.4.1 Natural history of EDSS state progression

The ERG notes that the company approach to modelling the natural history for EDSS state progression involves adjusting data from the British Columbia MS register by acceleration factors for the RES-RRMS and SOT-RRMS subgroups. These acceleration factors have been estimated using data from the placebo arm of the CLARITY trial using the 6-month CDP hazard rate at 96 week, i.e., by calculating the difference between the RES-RRMS and non RES-RRMS subgroups, and between the SOT-RRMS and non SOT-RRMS subgroups. The ERG considers that, whilst there is no clear alternative, this is a simplistic approach that is reliant on hazards being proportional for 6-month CDP between the RES-RRMS and non RES-RRMS, and between the SOT-RRMS and non SOT-RRMS subgroups. If the hazards are not proportional then the approach may over or underestimate the rate of disease progression in the model. Failure to test the validity of the PH assumption further adds to the uncertainty around the validity of the submitted model results.

5.4.2 Clinical effectiveness

The statistical evidence on clinical effectiveness from the CLARITY trial for qualifying ARR and 6-month CDP for the RES-RRMS and SOT-RRMS subgroups is provided in

Table 70.

Table 70 Time to 6-month CDP and qualifying ARR in CLARITY trial post-hoc subgroup analyses

	Cladribine tablets	Placebo
RES-RMMS		
6-month CDP: K-M estimate of progression-free patients, % (95% CI)	[redacted]	[redacted]
HR for cladribine tablets vs placebo (95% CI)	[redacted]	
SOT-RRMS		
6-month CDP K-M estimate of progression-free patients, % (95% CI)	[redacted]	[redacted]
HR for cladribine tablets vs placebo (95% CI)	[redacted]	
RES-RMMS		
Qualifying ARR (95% CI)	[redacted]	[redacted]
Rate ratio (95% CI)	[redacted]	
SOT-RMMS		
Qualifying ARR (95% CI)	[redacted]	[redacted]
Rate ratio (95% CI)	[redacted]	

RES=rapidly-evolving severe; RRMS=relapsing-remitting multiple sclerosis; SOT=sub-optimal therapy; ARR=annualised relapse rate; CI=confidence interval; K-M=Kaplan-Meier; CDP=confirmed disease progression
Source: CS, adapted from Table 30 and Table 35

RES-RRMS

Inevitably, there is considerable uncertainty around the reliability of point estimate results from analyses of small datasets, and interpretation of the associated wide credible/confidence intervals is problematic. Results from analyses of CLARITY trial data show that, at 2 years, people retrospectively described as having RES-RRMS who were treated with cladribine tablets had statistically significantly better qualifying ARR than those receiving placebo. However, results from analyses of 6-month CDP data from this population show that there is no statistically significant difference in effect between arms. This is not surprising given that clinical advice to the ERG is that there is no relationship between relapse frequency and disability progression. However, the ERG highlights that this effect may be due to the RES-RRMS definition used by the company; the company's definition relates to people with two or more relapses, not two or more *disabling* relapses, the wording used in previous submissions.[17,72] The ERG notes that, for patients who had been experiencing frequent disabling relapses, reducing qualifying ARR could, by default, also reduce disability progression. The ERG considers that data to support the conclusion that treatment with cladribine tablets is more effective than placebo in the population with RES-RRMS are limited to qualifying ARR only.

If only qualifying ARR effectiveness for cladribine tablets compared to placebo is included in the model, results show that treatment with cladribine tablets is dominated by alemtuzumab

and is less costly but generates fewer QALYs versus natalizumab (an ICER of £32,997 per QALY **lost** with cladribine tablets) or daclizumab (an ICER of £2,167 per QALY **lost** with cladribine tablets).

SOT-RRMS

Results from analyses of CLARITY trial data show that, at 2 years, for people retrospectively described as having SOT-RRMS, there is no statistically significant difference in terms of either qualifying ARR or 6-month CDP between arms. There is, therefore, no statistical basis to suggest that treatment with cladribine tablets is more effective than placebo for this patient group. Where sample sizes from a trial are so small that there is no statistically significant evidence that the intervention is more effective than placebo, there is no robust basis on which to construct an economic model.

5.4.3 Comparators: clinical effectiveness evidence

The company undertook an NMA to generate evidence to enable the qualifying ARR associated with treatment with cladribine tablets to be compared with the qualifying ARRs associated with the comparator treatments included in the company's economic model. The company also undertook a meta-regression to provide comparative estimates of 6-month CDP for treatment with cladribine tablets versus all comparators. In Section 5.6, the ERG has set out methodological concerns about the robustness of both the NMAs and the meta-regression. Briefly, the ERG considers that the results of the company's NMAs and meta-regression analyses should be treated with caution for the following reasons:

- RES-RRMS and SOT-RRMS effectiveness data for cladribine tablets in the NMAs were based on post-hoc subgroup analyses
- RES-RRMS and SOT-RRMS were post-hoc classifications of patients in the CLARITY trial
- Definitions of RES-RRMS and SOT-RRMS may have differed between included trials in the network. Importantly, the definition for RES-RRMS used in the CLARITY trial does not specify that people had to have had a *disabling* relapse, a term that was used in definitions of RES-RRMS in previous NICE MS TA submissions.[17,72]
- The ERG was not able to extract the required information from published trial reports so was not able to replicate either the company's NMAs or meta-regression and, therefore, was unable to fully validate the findings reported in the CS.

The ERG highlights that even if the results from the company's statistical analyses were robust for both the RES-RRMS and SOT-RRMS subgroups, the credible intervals for 6-month CDP for all DMTs overlap and the point estimates are similar. Indeed, within the CS (p110) the company notes that results show that there is 'no therapy statistically dominating in terms of efficacy'.

Similarly, an examination of the risk ratios compared to placebo of qualifying ARR results for the SOT-RRMS subgroup shows that the point estimates for each DMT are close and reside within the credible intervals of every other DMT (see CS, Table 69).

The picture is slightly less clear for the RES-RRMS subgroup. The qualifying ARR point estimates for the rate ratio compared to placebo for cladribine tablets, alemtuzumab and daclizumab are further apart than those for the SOT-RRMS subgroup but still reside in each other's credible intervals (CS, Table 69), with the point estimate for natalizumab only residing in the alemtuzumab credible interval.

The ERG considers that, in situations where confidence/credible intervals overlap and point estimates are close, the appropriate approach is to assume that all treatment options have equal efficacy. As such, regardless of treatment, the ERG has assumed that the 6-month CDP normalised hazard ratios for all treatments are the same as those generated by the company's meta-regression for cladribine tablets, i.e., 0.489 for the RES-RRMS subgroup.

The ERG has assumed that the RES-RRMS population qualifying ARR is the same for all DMTs other than natalizumab (which has a risk ratio compared to placebo of 0.19), with the effect set to be the same as for cladribine tablets (i.e., risk ratio 0.31). This change has no effect on the company's base case cost effectiveness results, i.e., treatment with cladribine tablets dominates all of the other comparators.

For the SOT-RRMS subgroup, the ERG has also assumed equal qualifying ARR effectiveness for all DMTs, with the rate ratio again set equal to cladribine tablets (0.48). This change has no effect on the company's base case cost effectiveness results, i.e., treatment with cladribine tablets still dominates all other comparators.

5.4.4 Waning of treatment effect

The DMTs considered by the company all have different modes of action and are delivered in different ways. As stated in the CS (p110), previous NICE appraisals of drugs for treating MS have incorporated assumptions about the waning of drug efficacy over time. In the absence of long-term follow-up data, in previously submitted models, the waning of effectiveness over time has been assumed to be the same for all DMTs, namely 100% during the first 2 years, 75% between years 2 and 4, and 50% from year 5 onwards.

The company has carried out analyses of CLARITY-EXT data in an attempt to provide robust evidence about the extent to which the effect of cladribine tablets on 6-month CDP wanes over a 4-year time horizon. The ERG commends the company for trying to provide evidence rather than simply relying on assumptions but highlights two issues with their analysis:

1. The confidence intervals, from the ITT analysis, for the HRs used to support no waning between years 2 and 4 are wide and include a reduction in effectiveness between years 2 and 4 of 75%. There is therefore evidence that the waning for cladribine tablets is the same as has been assumed for other DMTs in previous appraisals.
2. The company's analysis of waning, that is presented in the CS, was only carried out using 6-month CDP data and the results are only available for the ITT population, not for the RES-RRMS and SOT-RRMS subgroups. During the clarification process, the ERG requested analyses of waning using 6-month CDP and qualifying ARR for the RES-RRMS and SOT-RRMS subgroups. The ERG commends the company for providing what was an extensive re-analysis in a timely fashion. For SOT-RRMS, the company stated in the clarification response that the numbers were too small (there were only two patients in the intervention/placebo arm) for the treatment-switching algorithm to be robustly applied (although this analysis was undertaken anyway). Therefore, for the SOT-RRMS subgroup, there is no evidence on the waning of effectiveness of cladribine tablets. For the RES-RRMS group, the numbers were larger, although still small (10 or fewer patients in the trial arms), with a small number of outcomes, meaning that the confidence intervals were even wider than those for the ITT population waning analysis. In line with the results of the ITT analysis, the confidence intervals included a reduction in effectiveness between years 2 and 4 of 75%.

Clinical advice to the ERG is that there is almost complete uncertainty around the extent and timing of any waning of treatment effect for people in the RES-RRMS and SOT-RRMS subgroups (or for any patients with MS) who receive any of the DMTs included in the company model, for the period beyond 2 years. Results from the analyses carried out by the company add some information to the evidence base, but only over a 4-year period and only for the whole CLARITY-EXT trial population (i.e., the information is not specific to the RES-RRMS and SOT-RRMS subgroups) with wide confidence intervals. The ERG considers that the evidence provided by the company is not strong enough to merit the application of a waning effect for cladribine tablets that is different from that used for the other DMTs. Setting all treatments to have the same waning effect (100% up to year 2, 75% over years 2 to 4 and 50% thereafter) has no effect on the company's base case cost effectiveness results, i.e., cladribine tablets dominate all the comparator treatments for the RES-RRMS and SOT-RRMS subgroups.

Adoption of the waning assumption used in previous STAs should not mask the complete uncertainty around the medium- to long-term efficacy of any of the DMTs. With a time horizon

of 50 years, modelled effectiveness is essentially based on an absence of any information for 48 out of 50 (96%) of those years. Given there is no robust evidence of treatment effectiveness waning (6-month CDP or qualifying ARR) over a 2-year period for all of the DMTs considered in this appraisal, small differences in medium- and long-term efficacy will have a significant impact on the relative cost effectiveness of different DMTs.

5.4.5 Treatment discontinuation

The company estimated annualised discontinuation rates for patients treated with fingolimod, natalizumab and daclizumab using data from 15 of the 18 studies included in their NMA (CS, p116). These estimates are based on all cause discontinuation rates over the whole included trial periods. The all cause annualised discontinuation rates used in the model considered during TA441[20] were taken from the main trial and applied to the whole time horizon; this approach was criticised by both the ERG and the AC who considered that this approach was unrealistic. Their rationale was that discontinuation rates associated with taking any DMT are likely to be higher during the first year than during subsequent years because, during the early stages of a trial, patients are more likely to discontinue treatment due to AEs than during the later stages of the trial. The ERG and the AC for TA441[20] considered that it would be more appropriate to apply the discontinuation rates that occurred during the last year, rather than the first year, of a trial over the whole model time horizon. The ERG accepts that it was inappropriate to apply all cause annualised discontinuation rates for natalizumab and daclizumab that were derived over the whole trial period. However, in a scenario with only one line of treatment (as in this and previous MS submissions), with no alternative treatment to move onto, clinical advice to the ERG is that treatment would only stop when there was perceived to be no further clinical benefit to a patient even if a patient was still having relapses. The ERG considers that a more realistic approach to modelling discontinuation is, therefore, to use trial treatment discontinuation rates where available and then assume treatment would continue whilst the patient receives benefit, which, in the company model, is up until a patient reaches EDSS state 7.

This change in modelling approach increases both the costs and QALYs associated with treatment with natalizumab and daclizumab for both the RES-RRMS and SOT-RRMS subgroups. However, this change in discontinuation assumption has no effect on the company's base case cost effectiveness results i.e., for both the RES-RRMS and SOT-RRMS subgroups, treatment with cladribine tablets dominate all the comparator treatments.

5.4.6 Re-exposure to cladribine tablets and alemtuzumab

During TA441[20] and TA312[19] re-initiation rates for alemtuzumab following relapse in years 3 to 5 were included in the company's economic analysis. Reflecting this, the company model

incorporates rates of re-exposure to alemtuzumab that are equal to those used in TA441[20] and TA312,[19] whilst re-exposure rates for cladribine tablets are based on the company's projection of relapse rates for patients on cladribine tablets. Clinical advice to the ERG is that patients may be re-exposed to alemtuzumab after relapse but there is no published evidence to show whether this approach is effective. The way in which the company has modelled the effect of re-exposure means that re-exposure increases the costs of treatment and administration as well as the costs and QALY losses that arise from AEs; however, reflecting the absence of effectiveness evidence on re-exposure, this approach does not influence rates of qualifying ARR or 6-month CDP. As such, the ERG considers that it is more appropriate to remove re-exposure to cladribine tablets and alemtuzumab from the base case analyses. This isolated change reduces the costs and increases the QALYs associated with treatment with both cladribine tablets and alemtuzumab. However, there is no effect on the company's base case results, i.e. cladribine tablets dominate all the comparator treatments.

5.4.7 Adverse events

The ERG considers that the method used by the company to calculate the incidence of AEs included in the company model, whilst is well described for malignancies, is poorly described for several other AEs (such as gastrointestinal disorder and influenza). Reference is made in the CS to a series of NMAs, details of which are not included in the CS, that were used to calculate odds ratios for AEs for all DMTs compared to placebo. Although the values calculated for cladribine tablets produce AE rates that are comparable to those reported in the CLARITY trial, incidence rates reported in the CLARITY trial are for all patients with RRMS and do not specifically relate to the RES-RRMS and SOT-RRMS subgroups. The severity of events included in the NMAs to generate the AE rates is also unclear. This has implications for the validity of costs and disutilities associated with AEs. The ERG was not able to produce alternative AE rates for the DMTs considered in the model that were specific to the RES-RRMS and SOT-RRMS subgroups and thus the event rates, costs and disutility values associated with AEs that are used in the company model add further uncertainty to the cost effectiveness results.

5.4.8 EDSS state costs

The EDSS state costs presented in the CS are substantially higher than the costs used in previous MS STA submissions[17,18] and are also higher than the EDSS state costs that are used in a scenario analysis in the ongoing MS MTA (TA32).[15] A comparison of the different EDSS state costs used in selected previous submissions[17,18] to NICE, the ongoing MTA (TA32)[15] and in the CS is provided in Table 71.

Table 71 EDSS state costs used in NICE multiple sclerosis technology appraisal submissions

EDSS state	Costs			
	TA127[17] 2005/06 prices	TA320[18] (unit costs from TA127 updated to 2011/12 prices using the HCHS index)	Ongoing MTA (TA32)[15] (costs from TA320[18] inflated to 2015/16 using the HCHS index)	Cladribine tablets submission 2015/16 prices
0	£638	£903	£949	£2,729
1	£927	£939	£987	£2,615
2	£883	£688	£724	£2,415
3	£2,758	£3,765	£3,958	£2,365
4	£1,756	£1,824	£1,917	£9,625
5	£2,543	£3,094	£3,253	£9,629
6	£3,146	£4,130	£4,342	£9,937
7	£7,384	£10,871	£11,429	£36,753
8	£17,370	£26,478	£27,838	£38,824
9	£16,307	£21,187	£22,274	£38,824

EDSS state=Expanded Disability Status Scale; HCHS=Hospital and Community Health Services
Source: Email correspondence from NICE and company model

As shown in Table 71, the EDSS state costs in the cladribine tablets CS are substantially higher than the costs that have used in previous STAs[17,18] and in the ongoing MTA (TA32).[15] The bulk of the difference in these costs can be accounted for by the non-medical costs included in the current CS (derived from the analysis carried out by Karampampa[85]), specifically, the informal care element of professional and informal care estimated by Karampampa.[85]

The company argues that 80% of the costs of informal and professional care should be included in the economic evaluation as previous ACs have suggested that 80% of non-medical care would be paid for by PSS and, as such, this cost is relevant to the NICE reference case.[31]

Details of how the value of 80% was derived have not been provided; however, the ERG considers that this is likely to represent the proportion of professional domiciliary and personal care that is generally funded by PSS. However, professional domiciliary and personal care is not the same as informal care. This is exemplified by the fact that Karampampa[85] costed informal care by multiplying the hours of care provided by the average hourly wage rate in UK, whereas professional care was costed via unit costs reported by the PSSRU.[84] The ERG considers that only the professional care costs should have been included in the company

model as the costs of informal care are not met by PSS and are, therefore, not relevant to the NICE Reference Case.[31]

The ERG estimates that the informal care costs used in the company model amount to approximately £1,600 per year for EDSS state 0 to 3, £7,000 per year for EDSS state 4 to 6 and £17,000 per year for EDSS state 7 to 9, after the ERG adjusted the costs to 2015/16 prices. Excluding these informal care costs brings the costs of being in each EDSS state in line with the EDSS state costs used in previous STAs[17,18] and in the ongoing MTA (TA32).[15] The ERG, therefore, considers it appropriate to use the EDSS state costs used in the ongoing MTA (TA32)[15] updated to 2015/16 prices.

Using the MTA (TA32)[15] EDSS state costs substantially reduces the lifetime costs of all treatments by between 40% and 55%, with the greatest reductions seen for natalizumab and daclizumab. However, using the MTA (TA32)[15] values in isolation does not change the dominant position of cladribine tablets over all comparators for patients in the RES-RRMS and SOT-RRMS subgroups.

5.4.9 Health-related quality of life

The utilities incorporated into the company model are driven by EDSS state and are derived using data from the CLARITY trial and results from a literature review. Whilst the values are not specifically for patients with RES-RRMS or SOT-RRMS, the ERG considers that the primary driver of utility would be the EDSS state and so is satisfied that the values implemented in the company model are reasonable.

In addition to patient utility, carer utility is also incorporated into the company model by via a disutility applied to the carer that varies by the cared for patient's EDSS state. Whilst carers' utility has been included in previous submissions, the NICE reference case[31] states that outcomes should reflect all direct health effects, whether for patients or for other people. Whilst 'other people' could include carers, the NICE reference case[31] explicitly states that only the direct health effects of an intervention should be included in the analysis. The ERG considers that carers only benefit indirectly from any improvement in the EDSS state of a person taking DMTs and so their health outcomes should not be included.

Whilst reducing the QALYs gained for all treatments, removing carers' disutility from the model in isolation has no effect on the company's base case results, i.e., for both the RES-RRMS and SOT-RRMS subgroups, treatment with cladribine tablets dominates all the comparator treatments.

5.4.10 Time horizon

The company has assumed only a single line of treatment. This approach, which is one that has been adopted in previous NICE MS TAs, is acknowledged by the company to be unrealistic as, in NHS clinical practice, patients would be offered alternative DMTs at relapse or progression, or if treatment were stopped due to a lack of tolerability. As modelling of treatment sequencing is beyond the remit of the ERG, the ERG considers it informative to explore time horizons significantly shorter than lifetime to reflect the facts that (i) patients are unlikely to be on a single treatment for life and (ii) that the effectiveness data available for the DMTs are limited to, at the most, 4 years.

The ERG has produced analyses using time horizons of 2 years (the length of the CLARITY trial) and 4 years (the length of the CLARITY trial plus the length of the CLARITY-EXT trial).

For the RES-RRMS subgroup, use of a 2-year time horizon resulted in treatment with cladribine tablets remaining dominant compared to alemtuzumab, but being dominated by natalizumab. Compared to daclizumab, treatment with cladribine tablets generated an additional QALY gain of 0.005 at an incremental cost of £15,931, with an ICER of £3,121,856 per QALY gained. When a 4-year time horizon was used, treatment with cladribine tablets dominated all comparators.

For the SOT-RRMS subgroup, use of a 2-year time horizon resulted in treatment with cladribine tablets being dominant over alemtuzumab, but being dominated by daclizumab. Compared to fingolimod, treatment with cladribine tablets generated an additional QALY gain of 0.019 at an incremental cost of £16,977, with an ICER of £897,693 per QALY gained. When a 4-year time horizon was used, treatment with cladribine tablets dominated all comparators.

6 IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

A summary of the effects of the ERG's model amendments on the company's base case cost effectiveness results for the comparison of treatment with cladribine tables versus alemtuzumab, natalizumab and daclizumab for patients in the RES-RRMS subgroup are provided in Table 72 to Table 74.

For the RES-RRMS subgroup, none of the ERG's individual changes (except for shortening the time horizon) stop cladribine tablets from dominating all the other comparators. However, all of the ERG's individual changes (except stopping re-exposure to cladribine tablets or alemtuzumab) either reduce the cost savings or reduce the QALY gain associated with treatment with cladribine tablets compared to the other DMTs.

In the ERG scenario where treatment effectiveness for cladribine tablets compared with placebo is limited to qualifying ARR only (with effectiveness for alemtuzumab and daclizumab set equal to cladribine, as discussed in Section 5), then together with the other ERG model amendments over a 50-year time horizon:

- Treatment with cladribine tablets becomes dominated by alemtuzumab
- Treatment with cladribine tablets no longer dominates natalizumab, costing less (-£133,754) than natalizumab but generating fewer QALYs (-1.650) with an ICER per QALY **lost** of £81,050
- Treatment with cladribine tablets no longer dominates daclizumab, costing less (-£87,566) than daclizumab but generating fewer QALYs (-1.362) with an ICER per QALY **lost** of £64,269.

For interventions that are less costly and less effective (in terms of QALYs gained) than a comparator, the ICERs relate to the amount of money saved for every QALY that is lost by using the intervention rather than the comparator. When this is the case, an intervention will be considered cost effective if the ICER generated is **above** the willingness to pay threshold rather than below it. This contrasts with the common scenario in which treatment with an intervention results in higher costs and more QALYs than treatment with a comparator and the intervention is considered cost effective when the value of the ICER per QALY gained is lower than the willingness to pay threshold.

Table 72 Cost effectiveness results for cladribine tablets versus alemtuzumab with ERG revisions to company base case (list prices) – RES-RRMS

Model scenario and ERG revisions	Cladribine tablets		Alemtuzumab		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
Company base case	£480,441	8.098	£499,575	7.916	-£19,134	0.182	Cladribine dominant
R1a) For 6-month CDP, cladribine tablets have no effectiveness compared to placebo. For qualifying ARR, the effectiveness of alemtuzumab is set equal to the effectiveness of cladribine tablets	£567,079	6.251	£500,409	7.906	£66,670	-1.655	*Cladribine dominated*
R1b) For qualifying ARR and 6-month CDP, the effectiveness of alemtuzumab is set equal to the effectiveness of cladribine tablets	£480,441	8.098	£496,602	7.990	-£16,162	0.108	Cladribine dominant
R2) Waning effect: the effectiveness of cladribine tablets is set to 75% between years 2 and 4	£487,318	7.949	£499,575	7.916	-£12,257	0.033	Cladribine dominant
R3) No re-exposure to cladribine or alemtuzumab	£474,494	8.098	£491,747	7.916	-£17,253	0.182	Cladribine dominant
R4) Treatment discontinuation only at EDSS state 7 after 2 years	N/A	N/A	N/A	N/A	N/A	N/A	N/A
R5) TA32 EDSS state costs	£298,718	8.098	£314,615	7.916	-£15,897	0.182	Cladribine dominant
R6) No carer disutility	£480,441	9.943	£499,575	9.777	-£19,134	0.165	Cladribine dominant
R7) 2-year time horizon	£63,468	1.204	£72,796	1.200	-£9,328	0.004	Cladribine dominant
R8) 4-year time horizon	£81,567	2.272	£96,395	2.251	-£14,828	0.021	Cladribine dominant
(R1b-R6)	£297,128	9.807	£305,320	9.844	-£8,192	-0.037	£219,549*
(R1b-R7)	£56,817	1.343	£66,409	1.338	-£9,592	0.005	Cladribine dominant
(R1b-R6, R8)	£65,078	2.529	£74,567	2.527	-£9,490	0.002	Cladribine dominant
ERG scenario (R1a, R2-R6)	£346,045	8.227	£307,622	9.768	£38,423	-1.541	*Cladribine dominated*

CDP=confirmed disease progression; ARR=annualised relapse rate; DMT=disease-modifying treatment; QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio; N/A=not applicable

* The ICER represents the monetary gain per QALY lost rather than the cost per QALY gained

Table 73 Cost effectiveness results for cladribine tablets versus natalizumab with ERG revisions to company base case (list prices)– RES-RRMS

Model scenario & ERG revisions	Cladribine tablets		Natalizumab		Incremental		ICER £/QALY
	Cost	QALYs	Cost	QALYs	Cost	QALYs	
Company base case	£480,441	8.098	£611,117	7.586	-£130,676	0.512	Cladribine dominant
R1a) For 6-month CDP, cladribine tablets have no effectiveness compared to placebo	£567,079	6.251	£611,117	7.586	-£44,038	-1.335	£32,997*
R1b) For 6-month CDP, the effectiveness of natalizumab is set equal to the effectiveness of cladribine tablets	£480,441	8.098	£613,939	7.463	-£133,498	0.635	Cladribine dominant
R2) Waning effect: the effectiveness of cladribine tablets is set to 75% between years 2 and 4	£487,318	7.949	£611,117	7.586	-£123,799	0.363	Cladribine dominant
R3) No re-exposure to cladribine	£474,494	8.098	£611,117	7.586	-£136,623	0.512	Cladribine dominant
R4) Treatment discontinuation only at EDSS state 7 after 2 years for natalizumab	£480,441	8.098	£662,978	8.027	-£182,537	0.071	Cladribine dominant
R5) TA32 EDSS state costs	£298,718	8.098	£419,579	7.586	-£120,861	0.512	Cladribine dominant
R6) No carer disutility	£480,441	9.943	£611,117	9.462	-£130,676	0.480	Cladribine dominant
R7) 2-year time horizon	£63,468	1.204	£53,471	1.215	£9,997	-0.011	Cladribine dominated
R8) 4-year time horizon	£81,567	2.272	£101,063	2.268	-£19,496	0.004	Cladribine dominant
(R1b-R6)	£297,128	9.807	£478,521	9.720	-£181,393	0.087	Cladribine dominant
(R1b-R7)	£56,817	1.343	£46,878	1.349	£9,939	-0.006	*Cladribine dominated*
(R1b-R6, R8)	£65,078	2.529	£88,453	2.531	-£23,375	-0.002	£11,291,887*
ERG scenario (R1a, R2-R6)	£346,045	8.227	£479,799	9.877	-£133,754	-1.650	£81,050*

CDP=confirmed disease progression; ARR=annualised relapse rate; DMT=disease modifying treatment; QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio
*The ICER represents the monetary gain per QALY lost rather than the cost per QALY gained

Table 74 Cost effectiveness results for cladribine tablets versus daclizumab with ERG revisions to company base case (list prices)– RES-RRMS

Model scenario & ERG revisions	Cladribine tablets		Daclizumab		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
Company base case	£480,441	8.098	£569,623	7.174	-£89,182	0.924	Cladribine dominant
R1a) For 6-month CDP, cladribine tablets have no effectiveness compared to placebo. For qualifying ARR, the effectiveness of daclizumab is set equal to the effectiveness of cladribine tablets	£567,079	6.251	£569,092	7.180	-£2,013	-0.929	£2,167*
R1b) For qualifying ARR and 6-month CDP, the effectiveness of daclizumab is set equal to the effectiveness of cladribine tablets	£480,441	8.098	£569,973	7.152	-£89,532	0.946	Cladribine dominant
R2) Waning effect: the effectiveness of cladribine tablets is set to 75% between years 2 and 4	£487,318	7.949	£569,623	7.174	-£82,305	0.775	Cladribine dominant
R3) No re-exposure to cladribine	£474,494	8.098	£569,623	7.174	-£95,129	0.924	Cladribine dominant
R4) Treatment discontinuation only at EDSS state 7 after 2 years for daclizumab	£480,441	8.098	£622,959	7.708	-£142,518	0.390	Cladribine dominant
R5) TA32 EDSS state costs	£298,718	8.098	£370,829	7.174	-£72,110	0.924	Cladribine dominant
R6) No carer disutility	£480,441	9.943	£569,623	9.079	-£89,182	0.864	Cladribine dominant
R7) 2-year time horizon	£63,468	1.204	£47,537	1.199	£15,931	0.005	£3,121,856
R8) 4-year time horizon	£81,567	2.272	£87,551	2.226	-£5,984	0.046	Cladribine dominant
(R1b-R6)	£297,128	9.807	£433,490	9.546	-£136,363	0.261	Cladribine dominant
(R1b-R7)	£56,817	1.343	£40,550	1.341	£16,267	0.002	£7,206,437
(R1b-R6, R8)	£65,078	2.529	£74,817	2.510	-£9,739	0.020	Cladribine dominant
ERG scenario (R1a, R2-R6)	£346,045	8.227	£433,611	9.589	-£87,566	-1.362	£64,269*

CDP=confirmed disease progression; ARR=annualised relapse rate; DMT=disease-modifying treatment; QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio
*The ICER represents the monetary gain per QALY lost rather than the cost per QALY gained

A summary of the effects of the ERG's model amendments on the company's base case cost effectiveness results for the comparison of treatment with cladribine tables versus alemtuzumab, fingolimod and daclizumab for patients in the SOT-RRMS subgroup are provided in Table 75 to Table 77.

As discussed in Section 5, the ERG considers that, in the absence of statistically significant trial evidence to show that treatment with cladribine is more effective than placebo for patients with SOT-RRMS, there is no robust basis for any cost effectiveness results produced by an economic model. Table 75 to Table 77 do not include any cost effectiveness estimates based on an ERG scenario.

Table 75 Cost effectiveness results for cladribine tablets versus alemtuzumab with ERG revisions to company base case (list prices) – SOT-RRMS

Model scenario & ERG revisions	Cladribine tablets		Alemtuzumab		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
Company base case	£467,361	7.570	£484,910	7.417	-£17,549	0.153	Cladribine dominant
R1) For 6-month CDP and qualifying ARR the effectiveness of alemtuzumab is set equal to the effectiveness of cladribine tablets	£467,361	7.570	£480,655	7.507	-£13,294	0.063	Cladribine dominant
R2) Waning effect: the effectiveness of cladribine tablets is set to 75% between years 2 and 4	£471,434	7.484	£484,910	7.417	-£13,476	0.067	Cladribine dominant
R3) No re-exposure to cladribine tablets or alemtuzumab after 2 years	£461,531	7.570	£477,257	7.417	-£15,726	0.153	Cladribine dominant
R4) Treatment discontinuation only at EDSS 7 after 2 years	N/A	N/A	N/A	N/A	N/A	N/A	N/A
R5) TA32 EDSS costs	£289,050	7.570	£303,970	7.417	-£14,921	0.153	Cladribine dominant
R6) No carer disutility	£467,360	9.416	£484,910	9.274	-£17,550	0.142	Cladribine dominant
R7) 2-year time horizon	£65,644	1.135	£74,531	1.125	-£8,887	0.009	Cladribine dominant
R8) 4-year time horizon	£85,775	2.131	£99,937	2.108	-£14,162	0.023	Cladribine dominant
(R1-R6)	£285,791	9.336	£293,681	9.358	-£7,889	-0.021	£372,802*
(R1-R7)	£57,874	1.296	£66,648	1.290	-£8,774	0.006	Cladribine dominant
(R1-R6, R8)	£66,689	2.434	£75,400	2.430	-£8,711	0.004	Cladribine dominant

CDP=confirmed disease progression; ARR=annualised relapse rate; DMT=disease-modifying treatment; QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio
*The ICER represents the monetary gain per QALY lost rather than the cost per QALY gained

Table 76 Cost effectiveness results for cladribine tablets versus fingolimod with ERG revisions to company base case (list prices) – SOT-RRMS

Model scenario & ERG revisions	Cladribine tablets		Fingolimod		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
Company base case	£467,361	7.570	£539,427	6.626	-£72,065	0.944	Cladribine dominant
R1) For 6-month CDP and qualifying ARR the effectiveness of fingolimod is set equal to the effectiveness of cladribine tablets	£467,361	7.570	£528,912	6.941	-£61,552	0.629	Cladribine dominant
R2) Waning effect: the effectiveness of cladribine tablets is set to 75% between years 2 and 4	£471,434	7.484	£539,427	6.626	-£67,992	0.858	Cladribine dominant
R3) No re-exposure to cladribine	£461,531	7.570	£539,427	6.626	-£77,896	0.944	Cladribine dominant
R4) Treatment discontinuation only at EDSS 7 after 2 years for fingolimod	£467,360	7.570	£594,828	6.756	-£127,468	0.814	Cladribine dominant
R5) ID890 EDSS costs	£289,050	7.570	£343,415	6.626	-£54,366	0.944	Cladribine dominant
R6) No carer disutility	£467,360	9.416	£539,427	8.537	-£72,066	0.879	Cladribine dominant
R7) 2-year time horizon	£65,644	1.135	£48,668	1.116	£16,977	0.019	£897,693
R8) 4-year time horizon	£85,775	2.131	£88,813	2.048	-£3,038	0.083	Cladribine dominant
(R1-R6)	£285,791	9.336	£403,086	9.137	-£117,295	0.199	Cladribine dominant
(R1-R7)	£57,874	1.296	£40,480	1.296	£17,394	0.000	£37,479,159*
(R1-R6, R8)	£66,689	2.434	£73,331	2.420	-£6,642	0.013	Cladribine dominant

CDP=confirmed disease progression; ARR=annualised relapse rate; DMT=disease-modifying treatment; QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio
*The ICER represents the monetary gain per QALY lost rather than the cost per QALY gained

Table 77 Cost effectiveness results for cladribine tablets versus daclizumab with ERG revisions to company base case (list prices) – SOT-RRMS

Model scenario & ERG revisions	Cladribine tablets		Daclizumab		Incremental		ICER
	Cost	QALYs	Cost	QALYs	Cost	QALYs	£/QALY
Company base case	£467,361	7.570	£533,758	7.022	-£66,397	0.548	Cladribine dominant
R1) For 6-month CDP and qualifying ARR the effectiveness of daclizumab is set equal to the effectiveness of cladribine tablets	£467,361	7.570	£534,750	6.991	-£67,388	0.579	Cladribine dominant
R2) Waning effect: the effectiveness of cladribine tablets is set to 75% between years 2 and 4	£471,434	7.484	£533,758	7.022	-£62,323	0.462	Cladribine dominant
R3) No re-exposure to cladribine	£461,531	7.570	£533,758	7.022	-£72,227	0.548	Cladribine dominant
R4) Treatment discontinuation only at EDSS 7 after 2 years for daclizumab	£467,361	7.570	£590,474	7.359	-£123,112	0.211	Cladribine dominant
R5) TA32 EDSS state costs	£289,050	7.570	£345,024	7.022	-£55,974	0.548	Cladribine dominant
R6) No carer disutility	£467,361	9.416	£533,758	8.903	-£66,397	0.513	Cladribine dominant
R7) 2-year time horizon	£65,644	1.135	£48,359	1.136	£17,285	-0.001	*Cladribine dominated*
R8) 4-year time horizon	£85,775	2.131	£88,813	2.110	-£3,038	0.020	Cladribine dominant
(R1-R6)	£285,791	9.336	£408,028	9.172	-£122,237	0.164	Cladribine dominant
(R1-R7)	£57,874	1.296	£40,560	1.297	£17,314	0.000	*Cladribine dominated*
(R1-R6, R8)	£66,689	2.434	£74,439	2.423	-£7,749	0.010	Cladribine dominant

CDP=confirmed disease progression; ARR=annualised relapse rate; DMT=disease-modifying treatment; QALYs=quality adjusted life years; ICER=incremental cost effectiveness ratio
*The ICER represents the monetary gain per QALY lost rather than the cost per QALY gained

6.1 Conclusions of the cost effectiveness section

The ERG considers that the economic model submitted by the company is well designed and commends the company on the efforts that they have made to identify data with which to populate it.

However, the ERG considers that the usefulness of the model to decision makers is limited. The two major areas of concern are (i) uncertainty around the effectiveness of cladribine tablets versus placebo and versus other DMTs, and (ii) the inclusion of costs and benefits that are outwith the NICE reference case.[31] Whilst changes to the model can address the latter of these issues, no data are available to address the clinical evidence related issues.

Uncertainty around effectiveness

- The key limitations, in terms of generating cost effectiveness evidence using data from the CLARITY trial are:
    - Evidence has been generated using data from subgroups that have been defined post-hoc.
    - The sizes of the subgroup populations are very small, with only 50 and 17 patients receiving cladribine tablets in the RES-RRMS and SOT-RRMS subgroups respectively. This means that the samples have low power to detect statistically significant changes in outcomes.
    - The only outcome used in the company model that suggests that treatment with cladribine tablets is statistically significantly superior to placebo is qualifying ARR for the RES-RRMS subgroup.
    - There is no statistically significant evidence for patients in the SOT-RRMS subgroup that treatment with cladribine tablets is superior to placebo in terms of qualifying ARR or 6-month CDP (the two effectiveness outcomes used in the economic model). This means that any model results, for patients in the SOT-RRMS subgroup, showing that treatment with cladribine tablets is cost effective compared with any comparator should be viewed with caution.
- Evidence allowing the clinical effectiveness of cladribine tablets to be compared with other DMTs has been drawn from a set of NMAs and a meta-regression. The ERG was not able to extract the required information from published trial reports so was not able to replicate either the company's NMAs or meta-regression and, therefore, was unable to fully validate the findings reported in the CS (see Section 4.7).

- For qualifying ARR in the RES-RRMS subgroup, CLARITY trial data showed that cladribine tablets were demonstrated to be statistically significantly better than placebo. However, the results from the company's NMA show that the qualifying ARR confidence intervals for cladribine tablets and the other DMTs are wide. This makes the assessment of comparative effectiveness of cladribine tablets versus other DMTs essentially speculation.
- For 6-month CDP there is no evidence that cladribine tablets are any more (or less) effective than any other DMT for the RES-RRMS and SOT-RRMS subgroups over 2 years.
- Effectiveness evidence for all of the DMTs included in the company's economic analyses, for both the RES-RRMS and SOT-RRMS subgroups, is limited to 2 years. The company has then extrapolated this evidence out to 50 years. This means that there is no clinical evidence for 96% of the model time horizon. After 2 years, the modelling of waning of treatment effectiveness, treatment discontinuation rates and efficacy of re-exposure to cladribine tablets or alemtuzumab, all of which have an effect on clinical effectiveness, are all almost entirely based on assumptions.
- As in models that have informed previous NICE MS TAs, the model submitted by the company only considers a single line of treatment. In reality, upon relapse or treatment failure, other lines of treatment or re-exposure with a previous treatment would be offered to patients and, therefore, the model is overly simplistic. However, the ERG recognises that data to populate a more realistic lifetime model that includes multiple lines of treatment are not currently available.

The NICE reference case

- The NICE reference case[31] stipulates that outcomes should reflect all direct health effects, whether for patients or for other people. However, costs (in the form of lost income) and health benefits (in the form of disutility associated with EDSS states and progression) to carers are included in the company model. The ERG considers that carers' lost income is not a direct cost and that health benefits to carers cannot be considered to be direct health benefits from treatment with cladribine tablets and that, therefore, neither should have been included in the company model.

7 END OF LIFE CRITERIA

End of life considerations do not apply.

8 OVERALL CONCLUSIONS

8.1 Clinical: overall conclusions

Discrepancies between the evidence submitted and the final scope issued by NICE

The ERG considers that the evidence submitted by the company reflects the decision problem defined in the final scope issued by NICE for the RES-RRMS and SOT-RRMS populations only. The company did not provide evidence for people with RRMS who have not received previous treatment or for people with RRMS who have received previous treatment.

Direct clinical evidence

The company presented direct clinical effectiveness evidence (cladribine tablets versus placebo) from the CLARITY trial. This trial was of good quality and was well conducted. The RES-RRMS and SOT-RRMS subgroups and three outcomes (NEDA-3, time to 6-month CDP and proportion of people with 6-month CDP) were defined retrospectively. The ERG considers that the post-hoc definitions and analyses were necessary to address the final scope issued by NICE.

Indirect clinical evidence

The ERG considers that the company's general approach to undertaking NMAs and meta-regression) were appropriate in terms of the trials and comparators included, the statistical methodology employed, the model selection criteria, the choice of most appropriate model, and the interpretation of results. The results of the NMAs carried out by the company should be viewed with caution due to the paucity of data available for the key efficacy outcomes; particularly for alemtuzumab in the RES-RRMS and SOT-RRMS populations. The company also performed a meta-regression with the aim of estimating the efficacy of relevant DMTs compared to placebo in the RES-RRMS and SOT-RRMS. However, in light of the company's stated objectives, the ERG is not convinced that the results of the meta-regression presented by the company are valid or if the application of this meta-regression approach is appropriate.

8.2 Economics: overall conclusions

The effect of DMTs on slowing disability progression is by far the biggest driver of cost effectiveness in the economic model for cladribine tablets submitted by the company. The company and the ERG agree that, for 6-month CDP, evidence presented in the CS for the RES-RRMS and SOT-RRMS subgroups suggests that there is no difference between cladribine tablets and any of the other DMTs. The point estimates in the model for 6-month CDP are close for all DMTs. However, due to the company applying a lower treatment effect for waning to cladribine tablets compared with that applied to other DMTs, as well as significantly higher discontinuation rates for natalizumab, fingolimod and daclizumab,

cladribine tablets are shown to dominate all comparators. The ERG considers that even if key effectiveness evidence from the CLARITY trial was statistically significant versus placebo (which it is not for either RES-RRMS or SOT-RRMS), the waning and discontinuation rates applied in the model are not supported by evidence and are overestimating the cost effectiveness of cladribine tablets over other DMTs.

RES-RRMS

If cladribine tablets are ineffective at reducing 6-month CDP as suggested by the lack of statistically significant evidence from the CLARITY trial, but alemtuzumab, natalizumab and daclizumab are effective at reducing 6-month CDP with effectiveness parameters as estimated by the company meta-regression, then cladribine tablets would be dominated by alemtuzumab and be less costly and less effective than natalizumab and daclizumab, albeit at favourable ICERs per QALYs lost.

If cladribine tablets were assumed to be as effective at reducing 6-month CDP as suggested by the point estimate in the meta-regression, with alemtuzumab, natalizumab and daclizumab assumed to have equal effectiveness to cladribine tablets, then cladribine tablets would dominate natalizumab and daclizumab but would be less costly and less effective than alemtuzumab, again at a favourable ICER per QALY lost.

Given substantial uncertainties in the long-term evidence of all DMTs on disability progression and qualifying ARR, the ERG considers that any economic findings produced by the company model, even after ERG modifications, should be treated with caution.

SOT-RRMS

There is no statistically significant evidence of effectiveness of cladribine tablets over placebo in the SOT-RRMS subgroup for either 6-month CDP or qualifying ARR. There is therefore no basis on which to undertake economic analysis.

8.3 Implications for research

The ERG considers that:

- Currently, evidence does not allow a direct comparison of effectiveness of treatment with cladribine tablets versus any other DMT. A head-to-head trial considering these treatments and placebo would generate results that would be valuable to decision makers
- Future studies of people with RRMS should pay careful consideration to the classification of patient subgroups and use that classification as a randomisation stratification factor

- It would be useful to record, and report, HRQoL outcomes from any future clinical study of cladribine tablets and other DMTs. In particular, data should be collected, using the EQ-5D questionnaire, throughout the whole trial period, not only from patients whose disease has not progressed
- It would be useful to explore how cladribine tablets should be positioned in the treatment pathway.

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10 APPENDICES

10.1 Differences in statistical approaches for the original analysis and analysis for the CS of the CLARITY trial

The ERG notes several slight differences in numerical results presented within the CS compared to the results of efficacy outcomes reported in the CSR of the CLARITY trial and the primary publication which were prepared in 2010.[27]

The company state that within submissions to regulatory authorities including the present CS, the approach to handling missing data was amended to an approach the company consider more appropriate to the original approach specified within the TSAP. Additionally, original analyses were conducted with region as a fixed-effect within statistical models, however this fixed-effect was omitted from the re-analyses conducted for the CS, due to concerns regarding statistical model convergence within the smaller post-hoc subgroups.

Detailed reasons for the differences in the numerical results due to the differences in statistical modelling are presented in Table 78 and further details of the differences in the approach to missing data between the original analysis and the re-analysis of the CLARITY trial are provided in Table 79.

Table 78 Differences between reported results in primary publication and reported results in the CS for the CLARITY trial

CS Table	Estimate presented	Imputation and model used in the primary publication[27]	Imputation and model used in the CS
18	Qualifying ARR	- Numbers of qualifying relapses were imputed for rescued subjects (after the rescue time). - The relapse count was modelled through a Poisson regression model with fixed effects for treatment group and region and with log of time on study as an offset variable.	- Numbers of qualifying relapses were not imputed. Reported numbers of qualifying relapses were used for all subjects. - The relapse count was modelled through a Poisson regression model with fixed effect for treatment group and the log of time on study as an offset variable.
18	Time to first qualifying relapse Hazard Ratio (HR)	- The data for rescued subjects from the time of rescue onward was excluded from the analysis. - The time to first qualifying relapse was modelled through a Cox proportional hazards model with fixed effects for treatment group and region.	- The data for rescued subjects was not excluded from the analysis. - The time to first qualifying relapse was modelled through a Cox proportional hazards model with fixed effect for treatment group.
19	Proportion of relapse-free patients	- Missing data was imputed for the proportion of qualifying relapse-free subjects - The proportion of relapse-free patients was modelled through a logistic regression model with fixed effects for treatment group and region.	- Missing data was not imputed. The status of subjects who withdrew prematurely was considered "Unknown". - Only descriptive statistics are presented. - K-M estimates of proportions are brought in Table 18. For K-M estimation, subjects who withdrew prematurely were censored at the time of withdrawal.
20	Time to 3-month confirmed disability progression Hazard Ratio (HR)	- The data for rescued subjects from the time of rescue onward was excluded from the analysis. - The time to 3-month confirmed disability progression was modelled through a Cox proportional hazards model with fixed effects for treatment group and region.	- The data for rescued subjects was not excluded from the analysis. - The time to 3-month confirmed disability progression was modelled through a Cox proportional hazards model with fixed effect for treatment group.
21	Proportion of patients with 3-month confirmed disability progression	- Missing data was imputed for the proportion of patients without a 3-month sustained disability progression - The proportion of patients without a 3-month sustained disability progression was modelled through a logistic regression model with fixed effects for treatment group and region.	- Missing data was not imputed. The status of subjects who withdrew prematurely was considered "Unknown". - Only descriptive statistics are presented. - K-M estimates of proportions are brought in Table 20. For K-M estimation, subjects who withdrew prematurely were censored at the time of withdrawal.

ARR=annualised relapse rate; CS=company submission; K-M=kaplan-meier;
Source; adapted from company response to ERG clarification letter;

Table 79 Differences in analysis of missing data in the original analysis and the re-analysis of the CLARITY trial

TSAP page number	Original CLARITY analysis	CLARITY reanalysis for CS
p130-131	Imputation of number of qualifying relapses after rescue for subjects who received rescue medications	For all subjects, including those who received rescue medications, their reported qualifying relapses were used without exclusions or alterations.
p131-132	Imputation of missing data for the proportion of qualifying relapse-free subjects during 96 weeks (for subjects who prematurely withdrew from the study and had not had a relapse before withdrawing)	Subjects with no qualifying relapses but who withdrew from the study early were considered of unknown status and were excluded from logistic regression analyses (in the CS analyses). In the CS analyses, the proportions were presented descriptively and in addition, K-M estimates were provided (in which subjects that withdrew prematurely without having had a qualifying relapse were considered censored at the time of withdrawal).
p132	Imputation of missing data for the proportion of subjects without a 3-month sustained change in EDSS score (for subjects who prematurely withdrew from the study and had not had a sustained change before withdrawing)	The same approach as for the proportion of qualifying relapse-free subjects was taken.
p132	Imputation of missing data for the proportion of subjects with no CU, no active T1 Gd+ or no active T2 lesions (for subjects with missing mean lesion numbers)	For proportion of subjects with no active T1 Gd+ lesions and for proportion of subjects with no active T2 lesions: the same approach as for the proportion of qualifying relapse-free subjects was taken. The proportion of subjects with no CU lesions was analysed descriptively only in the CS analyses.
p132-133	Missing MRI data (baseline data and follow-up data)	Missing data were not imputed. For the definition of HDA populations: subjects with missing baseline number of T2 lesions were considered in the <9 T2 lesions category. Subjects with missing baseline number of T1 Gd+ lesions were considered in the <1 T1 Gd+ category.

CS=company submission; CU=combined unique; EDSS=expanded disability status scale Gd+=gadolinium enhancing; HDA=high disease activity; K-M=kaplan-meier;
Source; adapted from company response to ERG clarification letter; TSAP (p130-133)

10.2 Trials and participants included in network meta-analyses

Summary results and treatment networks for key efficacy outcomes ARR, 3-month CDP at 24 months and 6-month CDP at 24 months are provided in this section.

Table 80 Summary of trials used in the network meta-analysis for ARR (ITT population)

Study	Treatment 1	Events 1	Person years 1	Treatment 2	Events 2	Person years 2	Treatment 3	Events 3	Person years 3	Number of arms
ADVANCE trial	Placebo	181	445.25	INF-β-1a (Plegridy)	116	435.74	NA	NA	NA	2
AFFIRM trial	Placebo	472	738	Natalizumab, 300mg, q4w	294	1338	NA	NA	NA	2
BECOME trial	GA, 20mg, qd	23	69.7	INF-β-1b (Betaferon)	25	67.57	NA	NA	NA	2
BEYOND trial	GA, 20mg, qd	374	1099.5	INF-β-1b (Betaferon)	814	2260	NA	NA	NA	2
Bornstein 1987	Placebo	62	46	GA, 20mg, qd	16	47	NA	NA	NA	2
BRAVO trial	Placebo	275	808.82	INF-β-1a (Avonex)	215	826.92	NA	NA	NA	2
Calabrese 2012	GA, 20mg, qd	52	103	INF-β-1a (Avonex)	51	102	INF-β-1a (Rebif 44µg)	40	101	3
CARE-MS I trial	Alemtuzumab, 12mg, qd	119	661.11	INF-β-1a (Rebif 44µg)	122	312.82	NA	NA	NA	2
CARE-MS II trial	Alemtuzumab, 12mg, qd	236	907.69	INF-β-1a (Rebif 44µg)	201	386.54	NA	NA	NA	2
CombiRx trial	GA, 20mg, qd	70	650.7	INF-β-1a (Avonex)	97	604.4	NA	NA	NA	2
CONFIRM trial	Placebo	212	561.43	DMF, 240mg, bid	124	552.99	GA, 20mg, qd	163	569.62	3
Copolymer1 trial	Placebo	210	250	GA, 20mg, qd	161	272.88	NA	NA	NA	2
Decide Trial	Daclizumab , 150mg, q4w	500	2274.17	INF-β-1a (Avonex)	873	2238.16	NA	NA	NA	2
DEFINE Trial	Placebo	246	612.35	DMF, 240mg, bid	128	628.61	NA	NA	NA	2
Etemadifar 2006	INF-β-1a (Avonex)	57	60	INF-β-1a (Rebif 44µg)	66	60	INF-β-1b (Betaferon)	65	60	3
European and Canadian Glatiramer trial	Placebo	91	75.21	GA, 20mg, qd	61	75.31	NA	NA	NA	2
EVIDENCE trial	INF-β-1a (Avonex)	195	304.2	INF-β-1a (Rebif 44µg)	165	304.71	NA	NA	NA	2

FREEDOMS II trial	Placebo	246	615	Fingolimod, 0.5mg, qd	131	623.81	NA	NA	NA	2
FREEDOMS trial	Placebo	359	897.5	Fingolimod, 0.5mg, qd	172	955.6	NA	NA	NA	2
Gala trial	Placebo	215	445.5	GA, 40mg, tiw	290	901	NA	NA	NA	2
Gate trial	Placebo	24	61.88	GA, 20mg, qd	182	512.26	NA	NA	NA	2
IFNB MS trial	Placebo	266	209.2	INF-β-1b (Betaferon)	173	207	NA	NA	NA	2
IMPROVE trial	Placebo	6	18.14	INF-β-1a (Rebif 44µg)	5	35.96	NA	NA	NA	2
INCOMIN trial	INF-β-1a (Avonex)	126	180	INF-β-1b (Betaferon)	95	190	NA	NA	NA	2
Kappos 2011	Placebo	16	24.38	INF-β-1a (Avonex)	9	24.84	NA	NA	NA	2
Knobler 1993	Placebo	5	2.8	INF-β-1b (Betaferon)	2	2.3	NA	NA	NA	2
MSCRG trial	Placebo	235	286	INF-β-1a (Avonex)	212	316	NA	NA	NA	2
O`Connor 2006	Placebo	33	40.85	Teriflunomide, 14mg, od	19	35.31	Teriflunomide, 7mg, od	24	41.19	3
PRISMS trial	Placebo	479	364	INF-β-1a (Rebif 22µg)	344	366	INF-β-1a (Rebif 44µg)	318	363	3
REFORMS trial	INF-β-1a (Rebif 44µg)	10	13.92	INF-β-1b (Betaferon)	7	14.61	NA	NA	NA	2
REGARD trial	GA, 20mg, qd	194	669.5	INF-β-1a (Rebif 44µg)	201	669.5	NA	NA	NA	2
Saida 2012	Placebo	27	27	Fingolimod, 0.5mg, qd	13	26.25	NA	NA	NA	2
SELECT trial	Placebo	88	191.3	Daclizumab , 150mg, q4w	43	204.8	NA	NA	NA	2
TEMSO trial	Placebo	335	620.37	Teriflunomide, 14mg, od	227	613.51	Teriflunomide, 7mg, od	233	629.73	3
TENERE Trial	INF-β-1a (Rebif 44µg)	29	126.09	Teriflunomide, 14mg, od	39	144.44	Teriflunomide, 7mg, od	63	143.18	3
TOWER trial	Placebo	296	592	Teriflunomide, 14mg, od	177	553.125	Teriflunomide, 7mg, od	235	602.56	3

FREEDOMS II trial	Placebo	246	615	Fingolimod, 0.5mg, qd	131	623.81	NA	NA	NA	2
TRANSFORMS trial	Fingolimod, 0.5mg, qd	89	423.81	INF-β-1a (Avonex)	179	416.28	NA	NA	NA	2
CLARITY trial	Placebo	252	741.1	Cladribine tablets	109	767.1	NA	NA	NA	2
Saida 2017	Placebo	36	20.7	Natalizumab, 300mg, q4w	11	21.39	NA	NA	NA	2

ARR=annualised relapse rate; bid=twice a day; DMF=dimethyl fumarate; GA=glatiramer acetate; µg=microgram; mg=milligram; od=once daily; qd=per day; q1w=once a week; q4w=every 4 weeks; tiw=thrice a week; INF- β= interferon-beta; ITT=intention to treat; NA=not applicable;
Source: Table A1.1, company response to ERG clarification letter

Table 81 Summary of trials used in the network meta-analysis for ARR (HDA-RRMS subgroup)

Study	Treatment	Comparator	RR	LCI	UCI
AFFIRM trial	Natalizumab, 300mg, q4w	Placebo	0.31	0.23	0.42
CONFIRM trial	DMF, 240mg, bid	Placebo	0.66	0.42	1.04
CONFIRM trial	GA, 20mg, qd	Placebo	0.80	0.53	1.22
DEFINE Trial	DMF, 240mg, bid	Placebo	0.45	0.30	0.67
FREEDOMS trial	Fingolimod, 0.5mg, qd	Placebo	0.37	0.27	0.51
TOWER trial	Teriflunomide, 7 mg, od	Placebo	0.68	0.49	0.94
TOWER trial	Teriflunomide, 14 mg, od	Placebo	0.55	0.39	0.79
TRANSFORMS trial	Fingolimod, 0.5mg, qd	INF-β-1a (Avonex)	0.52	0.37	0.73
CLARITY trial	Cladribine tablets	Placebo	0.35	0.24	0.50
CAMMS223 trial	Alemtuzumab, 12mg, qd	INF-β-1a (Rebif 44µg)	0.26	0.11	0.59
CARE-MS I trial	Alemtuzumab, 12mg, qd	INF-β-1a (Rebif 44µg)	0.53	0.37	0.67
CARE-MS II trial	Alemtuzumab, 12mg, qd	INF-β-1a (Rebif 44µg)	0.51	0.39	0.77
PRISMS trial (unpublished data)	INF-β-1a (Rebif 44µg)	Placebo	0.72	0.53	0.96

ARR=annualised relapse rate; bid=twice a day; DMF=dimethyl fumarate; GA=glatiramer acetate; µg=microgram; mg=milligram; od=once daily; qd=per day; q1w=once a week; q4w=every 4 weeks; tiw=thrice a week; HDA-RRMS= high disease activity relapsing remitting multiple sclerosis; INF- β= interferon-beta; LCI=lower bound of 95% confidence interval; RR=rate ratio; UCI=upper bound of 95% confidence interval
Source: Table A2.1, company response to ERG clarification letter

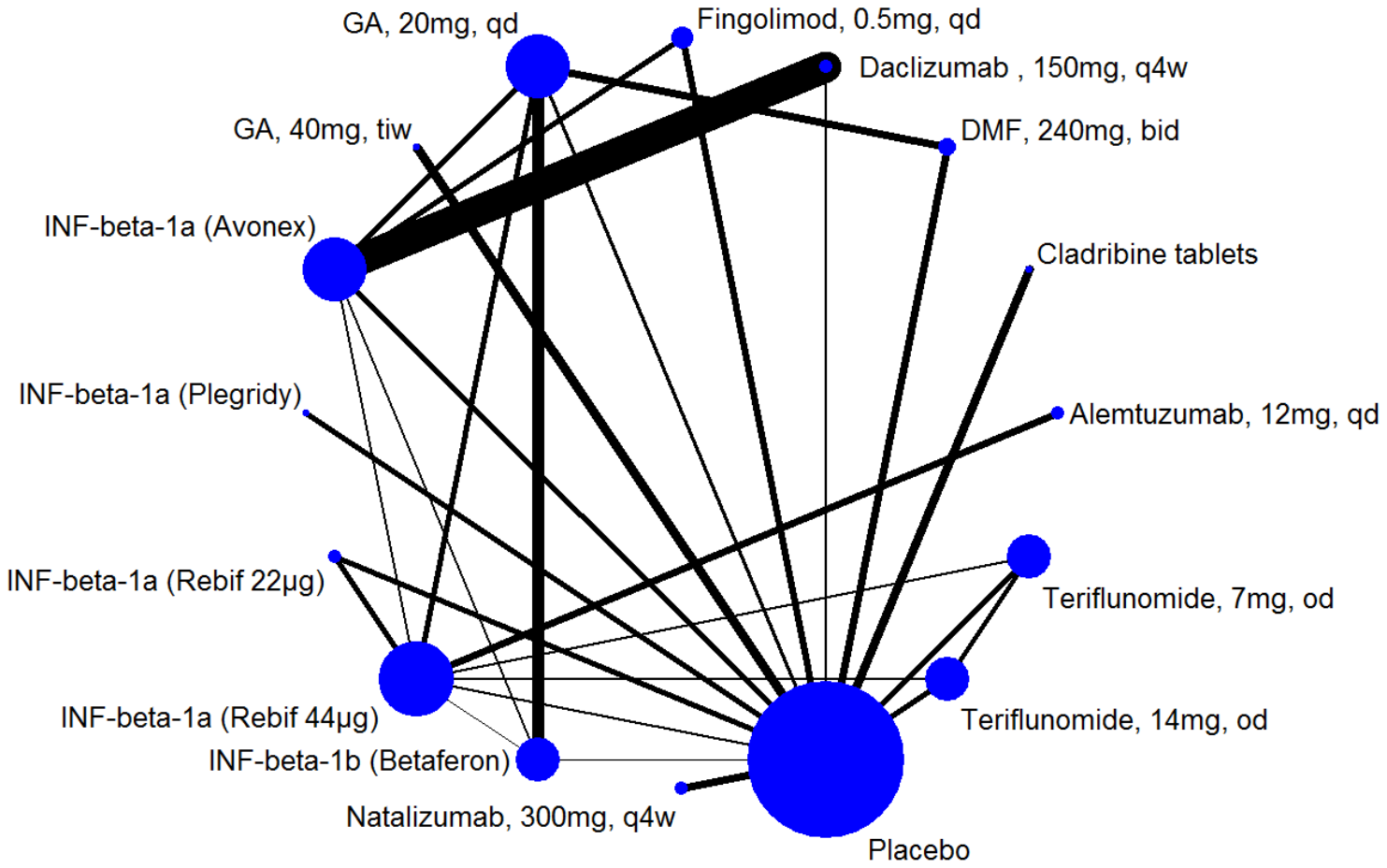

Figure 4 Network plot for the network meta-analysis of ARR (ITT population)

*Nodes of the network plot are weighted by the number of trials the intervention is included in, edges of the network plot are weighted by the total patient years contributing to the pairwise comparison.

ARR=annualised relapse rate; bid=twice a day; DMF=dimethyl fumarate; GA=glatiramer acetate; µg=microgram; mg=milligram; od=once daily; qd=per day; q1w=once a week; q4w=every 4 weeks; tiw=thrice a week; INF=interferon; ITT=intention to treat;
Source: produced by the ERG, based on the numbers of **Error! Reference source not found.**

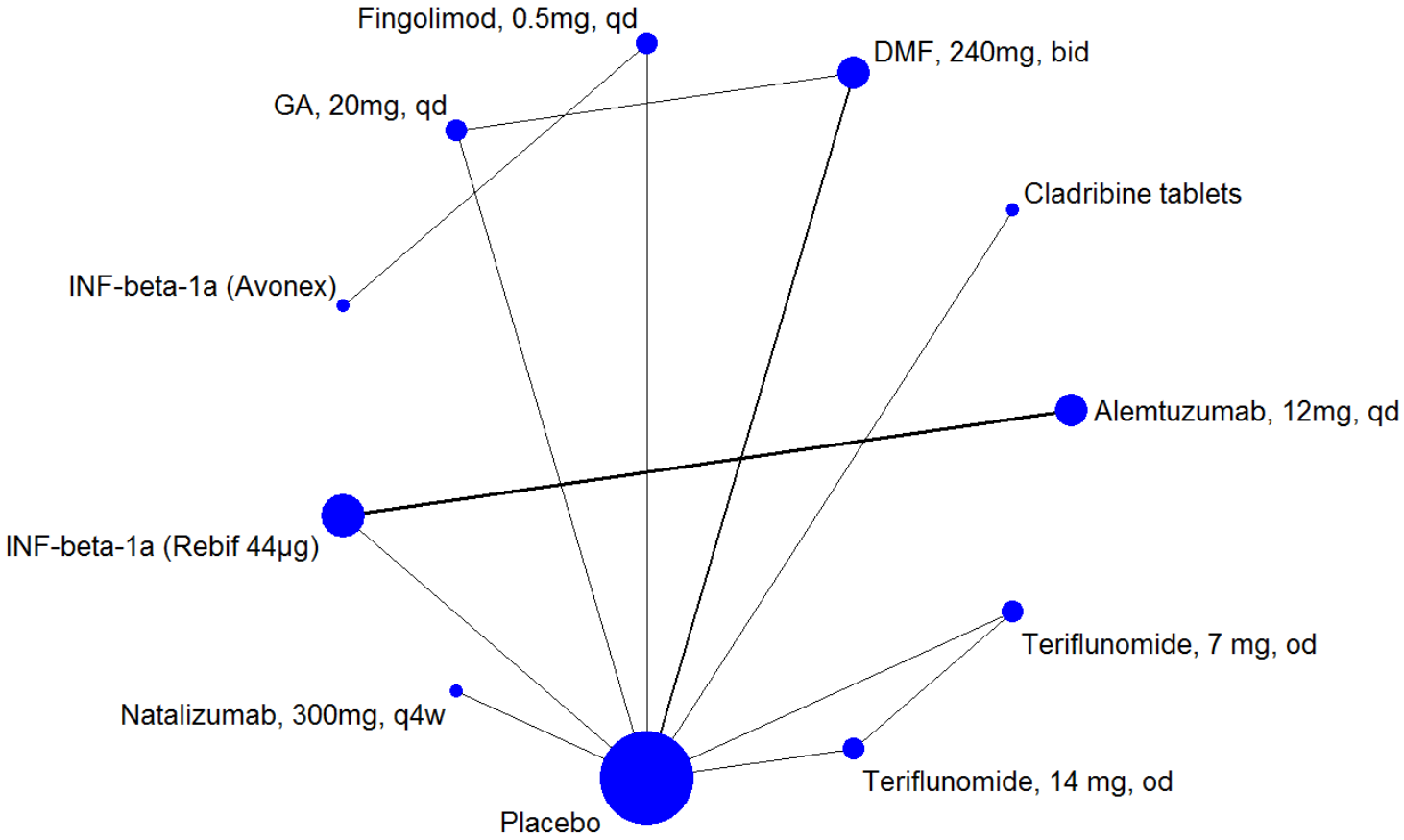

Figure 5 Network plot for the network meta-analysis of ARR (HDA-RRMS subgroup)

*Nodes of the network plot are weighted by the number of trials the intervention is included in, edges of the network plot are weighted by the standard error of the RR for each pairwise comparison.

ARR=annualised relapse rate; bid=twice a day; DMF=dimethyl fumarate; GA=glatiramer acetate; µg=microgram; mg=milligram; od=once daily; qd=per day; q1w=once a week; q4w=every 4 weeks; tiw=thrice a week; HDA-RRMS= high disease activity relapsing remitting multiple sclerosis; INF= interferon; RR=rate ratio.

Source: produced by the ERG, based on the numbers of Table 80 Summary of trials used in the network meta-analysis for ARR (ITT population)

Study	Treatment 1	Events 1	Person years 1	Treatment 2	Events 2	Person years 2	Treatment 3	Events 3	Person years 3	Number of arms
ADVANCE trial	Placebo	181	445.25	INF-β-1a (Plegridy)	116	435.74	NA	NA	NA	2
AFFIRM trial	Placebo	472	738	Natalizumab, 300mg, q4w	294	1338	NA	NA	NA	2
BECOME trial	GA, 20mg, qd	23	69.7	INF-β-1b (Betaferon)	25	67.57	NA	NA	NA	2
BEYOND trial	GA, 20mg, qd	374	1099.5	INF-β-1b (Betaferon)	814	2260	NA	NA	NA	2
Bornstein 1987	Placebo	62	46	GA, 20mg, qd	16	47	NA	NA	NA	2
BRAVO trial	Placebo	275	808.82	INF-β-1a (Avonex)	215	826.92	NA	NA	NA	2
Calabrese 2012	GA, 20mg, qd	52	103	INF-β-1a (Avonex)	51	102	INF-β-1a (Rebif 44µg)	40	101	3
CARE-MS I trial	Alemtuzumab, 12mg, qd	119	661.11	INF-β-1a (Rebif 44µg)	122	312.82	NA	NA	NA	2
CARE-MS II trial	Alemtuzumab, 12mg, qd	236	907.69	INF-β-1a (Rebif 44µg)	201	386.54	NA	NA	NA	2
CombiRx trial	GA, 20mg, qd	70	650.7	INF-β-1a (Avonex)	97	604.4	NA	NA	NA	2
CONFIRM trial	Placebo	212	561.43	DMF, 240mg, bid	124	552.99	GA, 20mg, qd	163	569.62	3
Copolymer1 trial	Placebo	210	250	GA, 20mg, qd	161	272.88	NA	NA	NA	2
Decide Trial	Daclizumab , 150mg, q4w	500	2274.17	INF-β-1a (Avonex)	873	2238.16	NA	NA	NA	2
DEFINE Trial	Placebo	246	612.35	DMF, 240mg, bid	128	628.61	NA	NA	NA	2
Etemadifar 2006	INF-β-1a (Avonex)	57	60	INF-β-1a (Rebif 44µg)	66	60	INF-β-1b (Betaferon)	65	60	3
European and Canadian Glatiramer trial	Placebo	91	75.21	GA, 20mg, qd	61	75.31	NA	NA	NA	2
EVIDENCE trial	INF-β-1a (Avonex)	195	304.2	INF-β-1a (Rebif 44µg)	165	304.71	NA	NA	NA	2

FREEDOMS II trial	Placebo	246	615	Fingolimod, 0.5mg, qd	131	623.81	NA	NA	NA	2
FREEDOMS trial	Placebo	359	897.5	Fingolimod, 0.5mg, qd	172	955.6	NA	NA	NA	2
Gala trial	Placebo	215	445.5	GA, 40mg, tiw	290	901	NA	NA	NA	2
Gate trial	Placebo	24	61.88	GA, 20mg, qd	182	512.26	NA	NA	NA	2
IFNB MS trial	Placebo	266	209.2	INF-β-1b (Betaferon)	173	207	NA	NA	NA	2
IMPROVE trial	Placebo	6	18.14	INF-β-1a (Rebif 44µg)	5	35.96	NA	NA	NA	2
INCOMIN trial	INF-β-1a (Avonex)	126	180	INF-β-1b (Betaferon)	95	190	NA	NA	NA	2
Kappos 2011	Placebo	16	24.38	INF-β-1a (Avonex)	9	24.84	NA	NA	NA	2
Knobler 1993	Placebo	5	2.8	INF-β-1b (Betaferon)	2	2.3	NA	NA	NA	2
MSCRG trial	Placebo	235	286	INF-β-1a (Avonex)	212	316	NA	NA	NA	2
O`Connor 2006	Placebo	33	40.85	Teriflunomide, 14mg, od	19	35.31	Teriflunomide, 7mg, od	24	41.19	3
PRISMS trial	Placebo	479	364	INF-β-1a (Rebif 22µg)	344	366	INF-β-1a (Rebif 44µg)	318	363	3
REFORMS trial	INF-β-1a (Rebif 44µg)	10	13.92	INF-β-1b (Betaferon)	7	14.61	NA	NA	NA	2
REGARD trial	GA, 20mg, qd	194	669.5	INF-β-1a (Rebif 44µg)	201	669.5	NA	NA	NA	2
Saida 2012	Placebo	27	27	Fingolimod, 0.5mg, qd	13	26.25	NA	NA	NA	2
SELECT trial	Placebo	88	191.3	Daclizumab , 150mg, q4w	43	204.8	NA	NA	NA	2
TEMSO trial	Placebo	335	620.37	Teriflunomide, 14mg, od	227	613.51	Teriflunomide, 7mg, od	233	629.73	3
TENERE Trial	INF-β-1a (Rebif 44µg)	29	126.09	Teriflunomide, 14mg, od	39	144.44	Teriflunomide, 7mg, od	63	143.18	3
TOWER trial	Placebo	296	592	Teriflunomide, 14mg, od	177	553.125	Teriflunomide, 7mg, od	235	602.56	3

FREEDOMS II trial	Placebo	246	615	Fingolimod, 0.5mg, qd	131	623.81	NA	NA	NA	2
TRANSFORMS trial	Fingolimod, 0.5mg, qd	89	423.81	INF-β-1a (Avonex)	179	416.28	NA	NA	NA	2
CLARITY trial	Placebo	252	741.1	Cladribine tablets	109	767.1	NA	NA	NA	2
Saida 2017	Placebo	36	20.7	Natalizumab, 300mg, q4w	11	21.39	NA	NA	NA	2

ARR=annualised relapse rate; bid=twice a day; DMF=dimethyl fumarate; GA=glatiramer acetate; µg=microgram; mg=milligram; od=once daily; qd=per day; q1w=once a week; q4w=every 4 weeks; tiw=thrice a week; INF- β= interferon-beta; ITT=intention to treat; NA=not applicable;
Source: Table A1.1, company response to ERG clarification letter

Table 81

Table 82 Summary of trials used in the network meta-analysis for ARR (RES-RRMS subgroup)

Study	Treatment	Comparator	RR	LCI	UCI
AFFIRM trial	Natalizumab, 300mg, q4w	Placebo	0.19	0.15	0.25
Decide Trial	Daclizumab , 150mg, q4w	INF-β-1a (Avonex)	0.42	0.31	0.57
FREEDOMS trial	Fingolimod, 0.5mg, qd	Placebo	0.37	0.24	0.57
TEMSO trial	Teriflunomide, 7mg, od	Placebo	0.51	0.32	0.81
TEMSO trial	Teriflunomide, 14mg, od	Placebo	0.81	0.51	1.28
TRANSFORMS trial	Fingolimod, 0.5mg, qd	INF-β-1a (Avonex)	0.48	0.24	0.95
CLARITY trial	Cladribine tablets	Placebo	0.31	0.18	0.53
CARE-MS I trial	Alemtuzumab	INF-β-1a (Rebif 44µg)	0.49	0.33	0.74
CARE-MS II trial	Alemtuzumab	INF-β-1a (Rebif 44µg)	0.51	0.35	0.74
SELECT trial	Daclizumab , 150mg, q4w	Placebo	0.48	0.22	1.04
PRISMS trial (unpublished data)	INF-β-1a (Rebif 44µg)	Placebo	0.44	0.21	0.91

ARR=annualised relapse rate; µg=microgram; mg=milligram; od=once daily; qd=per day; q1w=once a week; q4w=every 4 weeks; tiw=thrice a week; INF- β=interferon-beta; LCI=lower bound of 95% confidence interval; RES-RRMS=rapidly evolving severe relapsing remitting multiple sclerosis; RR=rate ratio; UCI=upper bound of 95% confidence interval
Source: Table A4.1, company response to ERG clarification letter

Table 83 Summary of trials used in the network meta-analysis for ARR (SOT-RRMS subgroup)

Study	Treatment	Comparator	RR	LCI	UCI
TRANSFORMS trial	Fingolimod, 0.5mg, qd	INF-β-1a (Avonex)	0.52	0.37	0.74
FREEDOMS trial	Fingolimod, 0.5mg, qd	Placebo	0.49	0.31	0.78
CLARITY trial	Cladribine tablets	Placebo	0.48	0.20	1.11

ARR=annualised relapse rate; mg=milligram; qd=per day; INF- β=interferon-beta; LCI=lower bound of 95% confidence interval; RR=rate ratio; SOT-RRMS=suboptimal therapy relapsing remitting multiple sclerosis; UCI=upper bound of 95% confidence interval
Source: Table A3.1, company response to ERG clarification letter

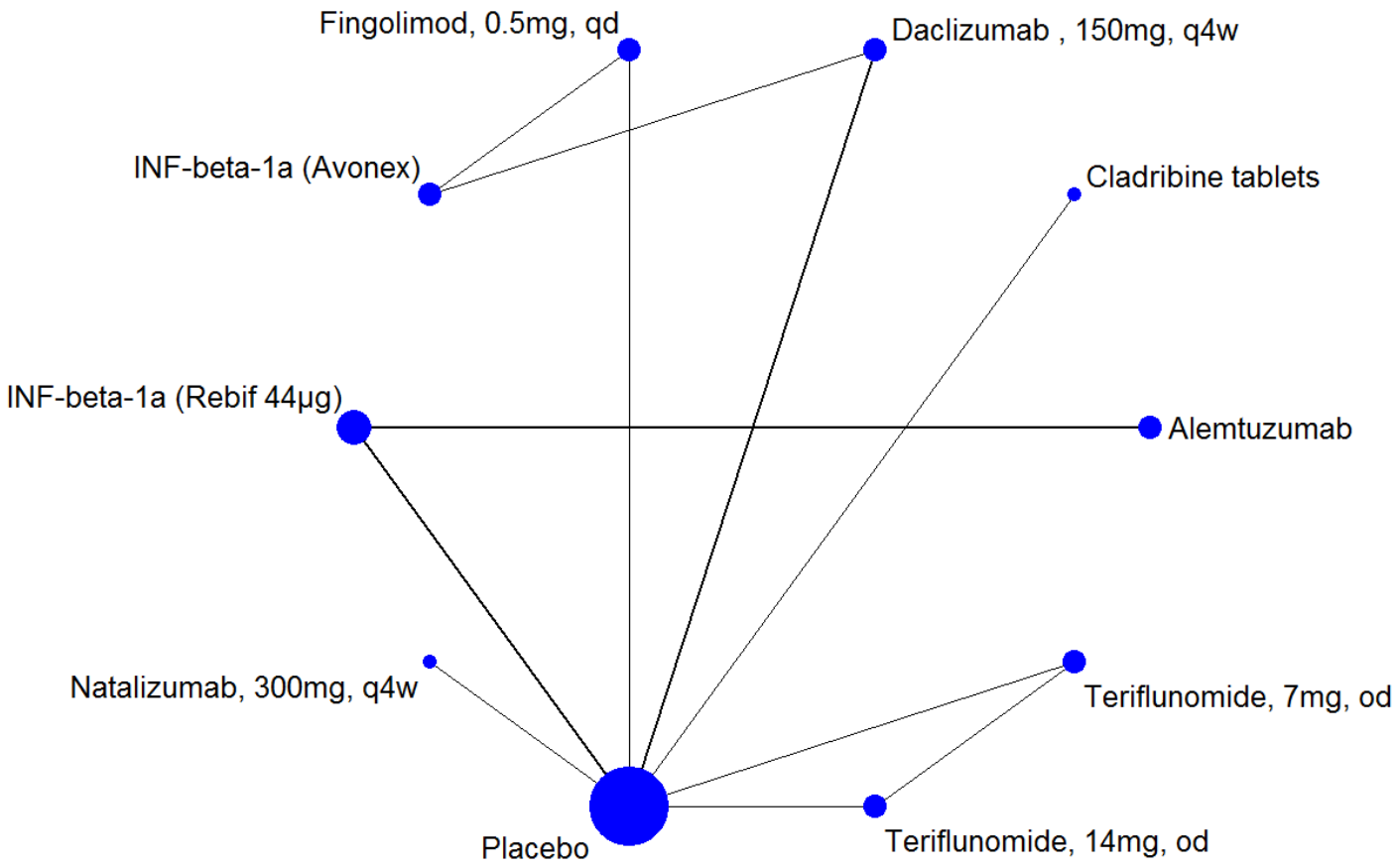

Figure 6 Network plot for the network meta-analysis of ARR (RES-RRMS subgroup)

*Nodes of the network plot are weighted by the number of trials the intervention is included in, edges of the network plot are weighted by the standard error of the RR for each pairwise comparison.

ARR=annualised relapse rate; µg=microgram; mg=milligram; od=once daily; qd=per day; q1w=once a week; q4w=every 4 weeks; tiw=thrice a week; INF=interferon; RES-RRMS=rapidly evolving severe relapsing remitting multiple sclerosis; RR=rate ratio;
Source: produced by the ERG, based on the numbers of Table 82

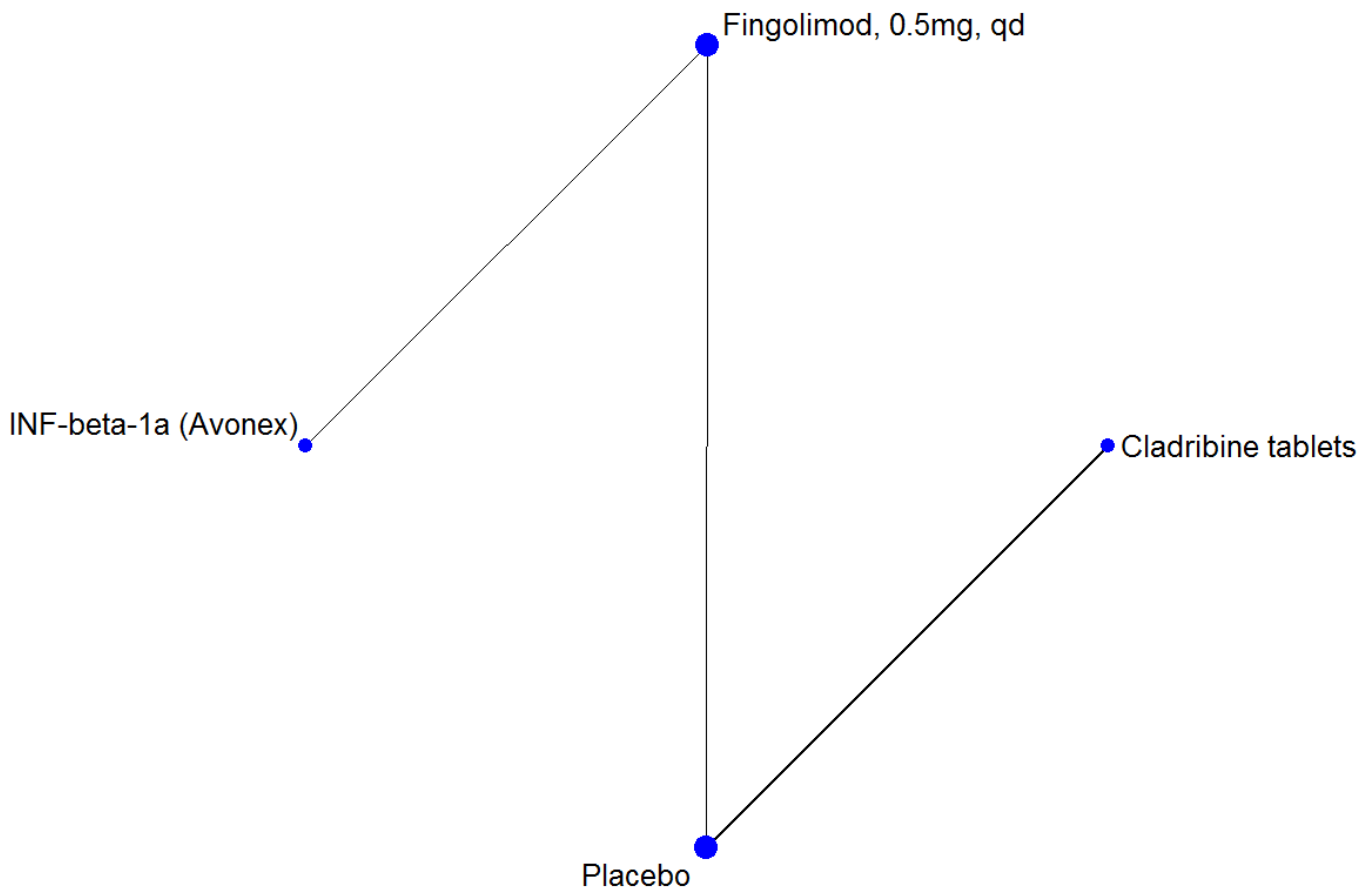

Figure 7 Network plot for the network meta-analysis of ARR (SOT-RRMS subgroup)

*Nodes of the network plot are weighted by the number of trials the intervention is included in, edges of the network plot are weighted by the standard error of the RR for each pairwise comparison.
ARR=annualised relapse rate; mg=milligram; qd=per day; INF=interferon; RR=rate ratio; SOT-RRMS=suboptimal therapy relapsing remitting multiple sclerosis;
Source: produced by the ERG, based on the numbers of Table 83

Table 84 Summary of trials used in the network meta-analysis for 3-month CDP at 24 months (ITT population)

Study	Treatment 1	Events 1	Total 1	Treatment 2	Events 2	Total 2	Treatment 3	Events 3	Total 3	Number of arms
AFFIRM trial	Placebo	91	315	Natalizumab, 300mg, q4w	107	627	NA	NA	NA	2
BEYOND trial	GA, 20mg, qd	92	448	INF-β-1b (Betaferon)	244	897	NA	NA	NA	2
Bornstein 1987	Placebo	11	25	GA, 20mg, qd	5	25	NA	NA	NA	2
BRAVO trial	Placebo	60	450	INF-β-1a (Avonex)	47	447	NA	NA	NA	2
CAMMS223 trial	Alemtuzumab, 12mg, qd	11	113	INF-β-1a (Rebif 44µg)	24	111	NA	NA	NA	2
CONFIRM trial	Placebo	62	363	DMF, 240mg, bid	47	362	GA, 20mg, qd	56	360	3
Copolymer1 trial	Placebo	31	126	GA, 20mg, qd	27	125	NA	NA	NA	2
Decide Trial	Daclizumab , 150mg, q4w	118	919	INF-β-1a (Avonex)	138	922	NA	NA	NA	2
DEFINE Trial	Placebo	89	410	DMF, 240mg, bid	57	411	NA	NA	NA	2
FREEDOMS II trial	Placebo	103	355	Fingolimod, 0.5mg, qd	91	358	NA	NA	NA	2
FREEDOMS trial	Placebo	101	418	Fingolimod, 0.5mg, qd	75	425	NA	NA	NA	2
IFNB MS trial	Placebo	56	123	INF-β-1b (Betaferon)	43	124	NA	NA	NA	2
PRISMS trial	Placebo	68	187	INF-β-1a (Rebif 22µg)	49	189	INF-β-1a (Rebif 44µg)	47	184	3
TEMSO trial	Placebo	99	363	Teriflunomide, 14mg, od	72	359	Teriflunomide, 7mg, od	79	366	3
TOWER trial	Placebo	76	389	Teriflunomide, 14mg, od	58	372	Teriflunomide, 7mg, od	86	408	3
CLARITY trial	Placebo	103	437	Cladribine tablets	65	433	NA	NA	NA	2

bid=twice a day; CDP=confirmed disability progression; DMF=dimethyl fumarate; GA=glatiramer acetate; µg=microgram; mg=milligram; od=once daily; qd=per day; q1w=once a week; q4w=every 4 weeks; tiw=thrice a week; INF- β= interferon-beta; ITT=intention to treat; NA=not applicable;
Source: Table A2.1, company response to ERG clarification letter

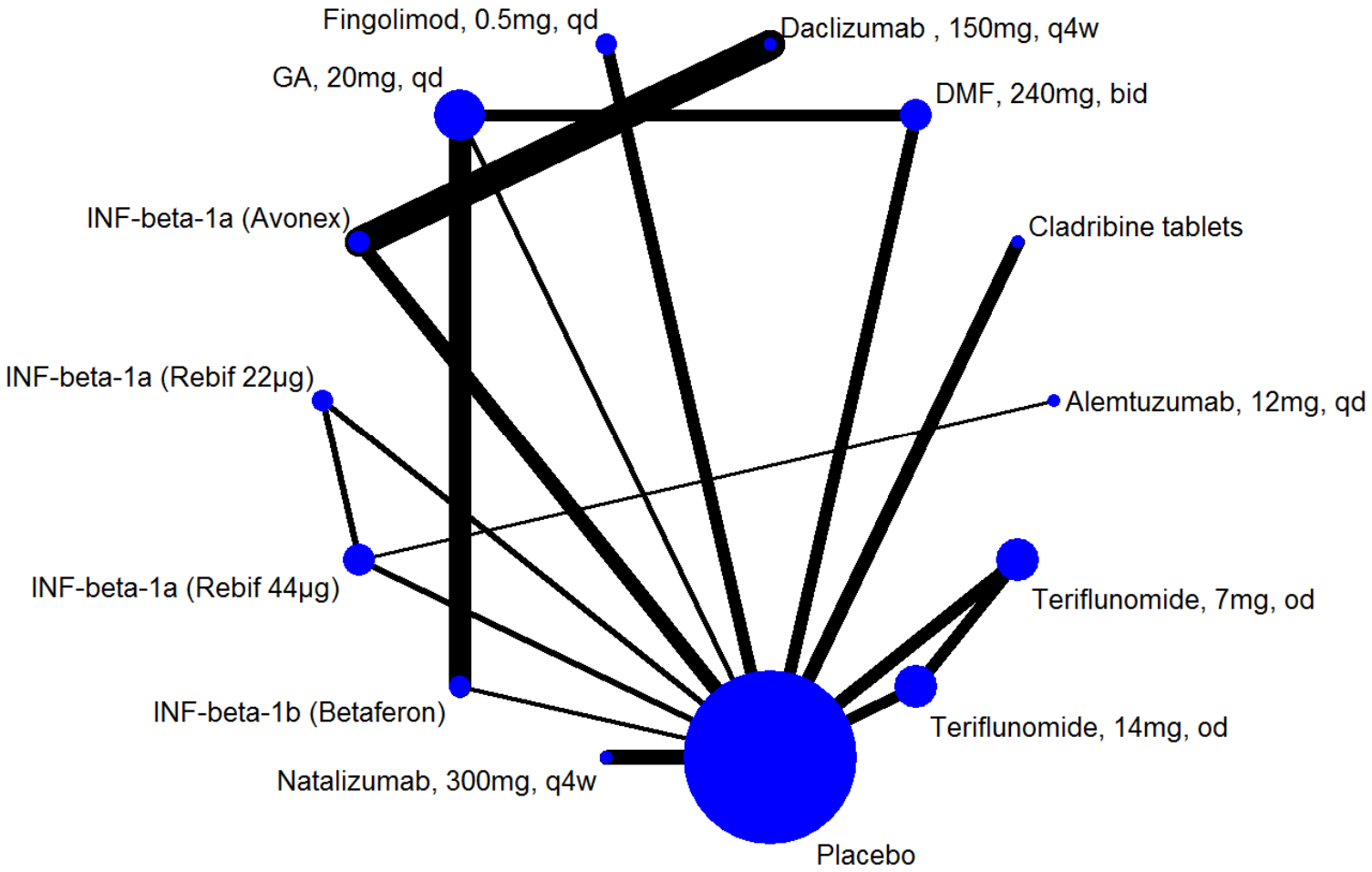

Figure 8 Network plot for the network meta-analysis of 3-month CDP at 24 months (ITT population)

*Nodes of the network plot are weighted by the number of trials the intervention is included in, edges of the network plot are weighted by the total number of participants for each pairwise comparison.
bid=twice a day; CDP=confirmed disability progression; DMF=dimethyl fumarate; GA=glatiramer acetate; µg=microgram; mg=milligram; od=once daily; qd=per day; q1w=once a week; q4w=every 4 weeks; tiw=thrice a week; INF= interferon; ITT=intention to treat;
Source: produced by the ERG, based on the numbers of Table 84

Table 85 Summary of trials used in the network meta-analysis for 3-month CDP at 24 months (HDA-RRMS subgroup)

Study	Treatment	Comparator	HR	LCI	UCI
AFFIRM trial	Natalizumab, 300 mg, q4w	Placebo	0.55	0.35	0.86
CONFIRM trial	DMF, 240 mg, bid	Placebo	0.62	0.30	1.28
CONFIRM trial	GA, 20 mg, qd	Placebo	0.44	0.20	0.95
DEFINE Trial	DMF, 240 mg, bid	Placebo	0.67	0.38	1.19
FREEDOMS trial	Fingolimod, 0.5 mg, qd	Placebo	0.62	0.37	1.04
CLARITY trial	Cladribine tablets	Placebo	0.28	0.15	0.53

bid=twice a day; CDP=confirmed disability progression; DMF=dimethyl fumarate; GA=glatiramer acetate; mg=milligram; qd=per day; q4w=every 4 weeks; HDA-RRMS= high disease activity relapsing remitting multiple sclerosis; HR=hazard ratio; INF- β= interferon-beta; LCI=lower bound of 95% confidence interval; UCI=upper bound of 95% confidence interval
Source: Table A2.2, company response to ERG clarification letter

Table 86 Summary of trials used in the network meta-analysis for 3-month CDP at 24 months (RES-RRMS subgroup)

Study	Treatments	Comparator	HR	LCI	UCI
AFFIRM trial	Natalizumab, 300mg, q4w	Placebo	0.47	0.24	0.93
CLARITY trial	Cladribine tablets	Placebo	0.77	0.34	1.74
FREEDOMS trial	Fingolimod, 0.5mg, qd	Placebo	0.78	0.36	1.68
TEMSO trial	Teriflunomide, 7 mg, od	Placebo	0.61	0.25	1.51
TEMSO trial	Teriflunomide, 14 mg, od	Placebo	0.65	0.26	1.59

CDP=confirmed disability progression; mg=milligram; od=once daily; qd=per day; q4w=every 4 weeks; HR=hazard ratio; LCI=lower bound of 95% confidence interval; RES-RRMS=rapidly evolving severe relapsing remitting multiple sclerosis; UCI=upper bound of 95% confidence interval
Source: Table A4.2, company response to ERG clarification letter

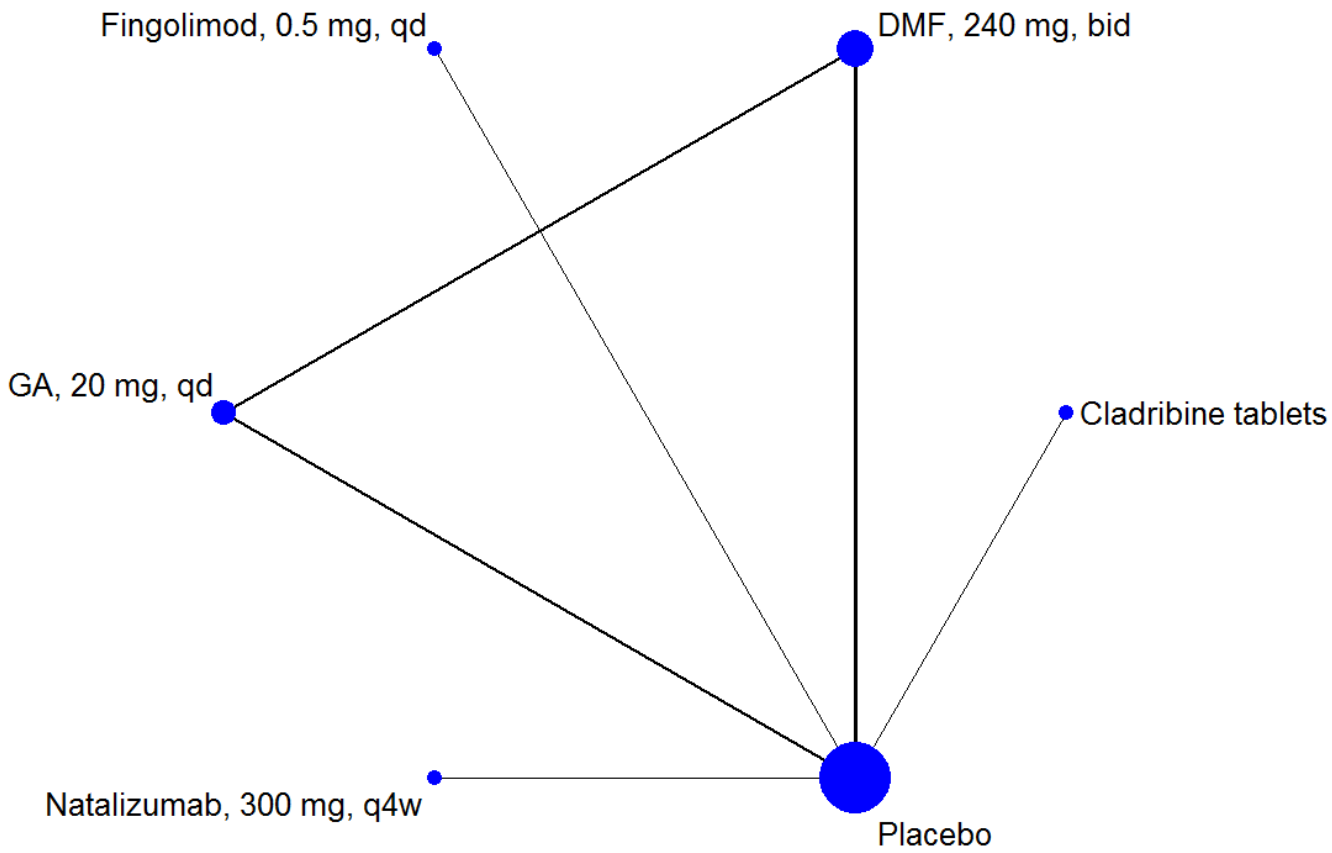

Figure 9 Network plot for the network meta-analysis of 3-month CDP at 24 months (HDA-RRMS subgroup)

*Nodes of the network plot are weighted by the number of trials the intervention is included in, edges of the network plot are weighted by the standard error of the HR for each pairwise comparison.
bid=twice a day; CDP=confirmed disability progression; DMF=dimethyl fumarate; GA=glatiramer acetate; mg=milligram; qd=per day; q4w=every 4 weeks; HDA-RRMS= high disease activity relapsing remitting multiple sclerosis; HR=hazard ratio; INF= interferon;
Source: produced by the ERG, based on the numbers of Table 85

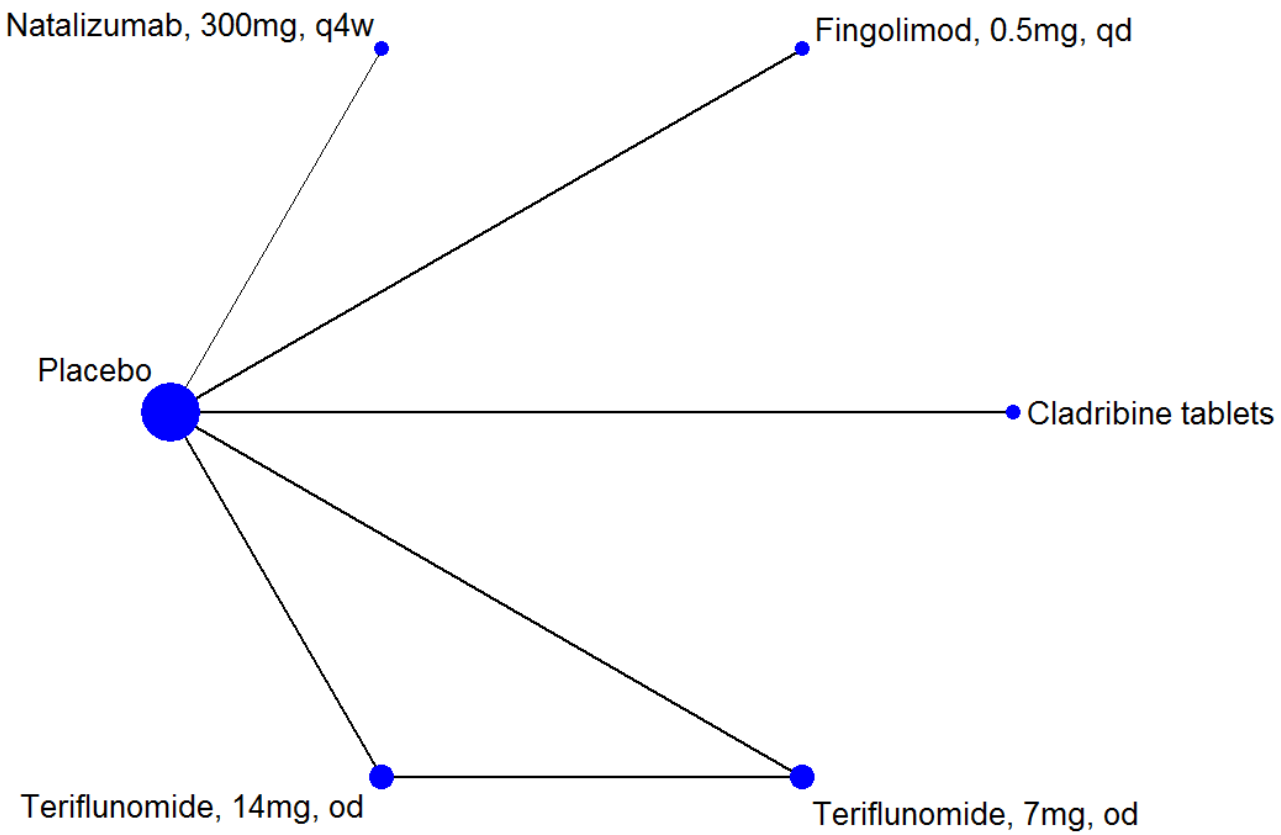

Figure 10 Network plot for the network meta-analysis of 3-month CDP at 24 months (RES-RRMS subgroup)

*Nodes of the network plot are weighted by the number of trials the intervention is included in, edges of the network plot are weighted by the standard error of the HR for each pairwise comparison.
CDP=confirmed disability progression; mg=milligram; od=once daily; qd=per day; q4w=every 4 weeks; HR=hazard ratio; RES-RRMS=rapidly evolving severe relapsing remitting multiple sclerosis;
Source: produced by the ERG, based on the numbers of Table 86

Table 87 Summary of trials used in the network meta-analysis for 6-month CDP at 24 months (ITT population)

Study	Treatment 1	Event 1	Total 1	Treatment 2	Event 2	Total 2	Treatment 3	Event 3	Total 3	Number of arms
AFFIRM trial	Placebo	72	315	Natalizumab	69	627	NA	NA	NA	2
BECOME trial	GA, 20 mg, qd	6	39	INF-β-1b (Betaferon)	4	36	NA	NA	NA	2
BRAVO trial	Placebo	46	450	INF-β-1a (Rebif 44µg)	35	447	NA	NA	NA	2
CAMMS223 trial	Alemtuzumab 12mg	4	113	INF-β-1a (Rebif 44µg)	19	111	NA	NA	NA	2
CARE-MS I trial	Alemtuzumab 12mg	30	386	INF-β-1a (Rebif 44µg)	21	195	NA	NA	NA	2
CARE-MS II trial	Alemtuzumab 12mg	54	436	INF-β-1a (Rebif 44µg)	43	231	NA	NA	NA	2
CONFIRM trial	Placebo	45	363	Dimethyl fumurate	28	362	GA, 20 mg, qd	38	360	3
Decide Trial	Daclizumab	83	919	INF-β-1a (Avonex)	111	922	NA	NA	NA	2
DEFINE	Placebo	69	410	Dimethyl fumurate	52	411	NA	NA	NA	2
FREEDOMS II trial	Placebo	63	355	Fingolimod	49	358	NA	NA	NA	2
FREEDOMS trial	Placebo	79	418	Fingolimod	53	425	NA	NA	NA	2
INCOMIN trial	INF-β-1a (Avonex)	28	92	INF-β-1b (Betaferon)	13	96	NA	NA	NA	2
MSCRG trial	Placebo	50	143	INF-β-1a (Avonex)	35	158	NA	NA	NA	2
REGARD trial	GA, 20 mg, qd	33	378	INF-β-1a (Rebif 44µg)	45	386	NA	NA	NA	2
TEMSO trial	Placebo	68	363	Teriflunomide 14mg	49	359	Teriflunomide 7mg	51	366	3
TOWER trial	Placebo	46	389	Teriflunomide 14mg	43	372	Teriflunomide 7mg	61	408	3
CLARITY trial	Placebo	[redacted]	[redacted]	Cladribine tablets	[redacted]	[redacted]	NA	NA	NA	2
PRISMS trial (unpublished data)	Placebo	[redacted]	[redacted]	INF-β-1a (Rebif 44µg)	[redacted]	[redacted]	NA	NA	NA	2

bid=twice a day; CDP=confirmed disability progression; DMF=dimethyl fumarate; GA=glatiramer acetate; µg=microgram; mg=milligram; od=once daily; qd=per day; q1w=once a week; q4w=every 4 weeks; tiw=thrice a week; INF- β= interferon-beta; ITT=intention to treat; NA=not applicable;
Source: CS, Appendix L, Table 60

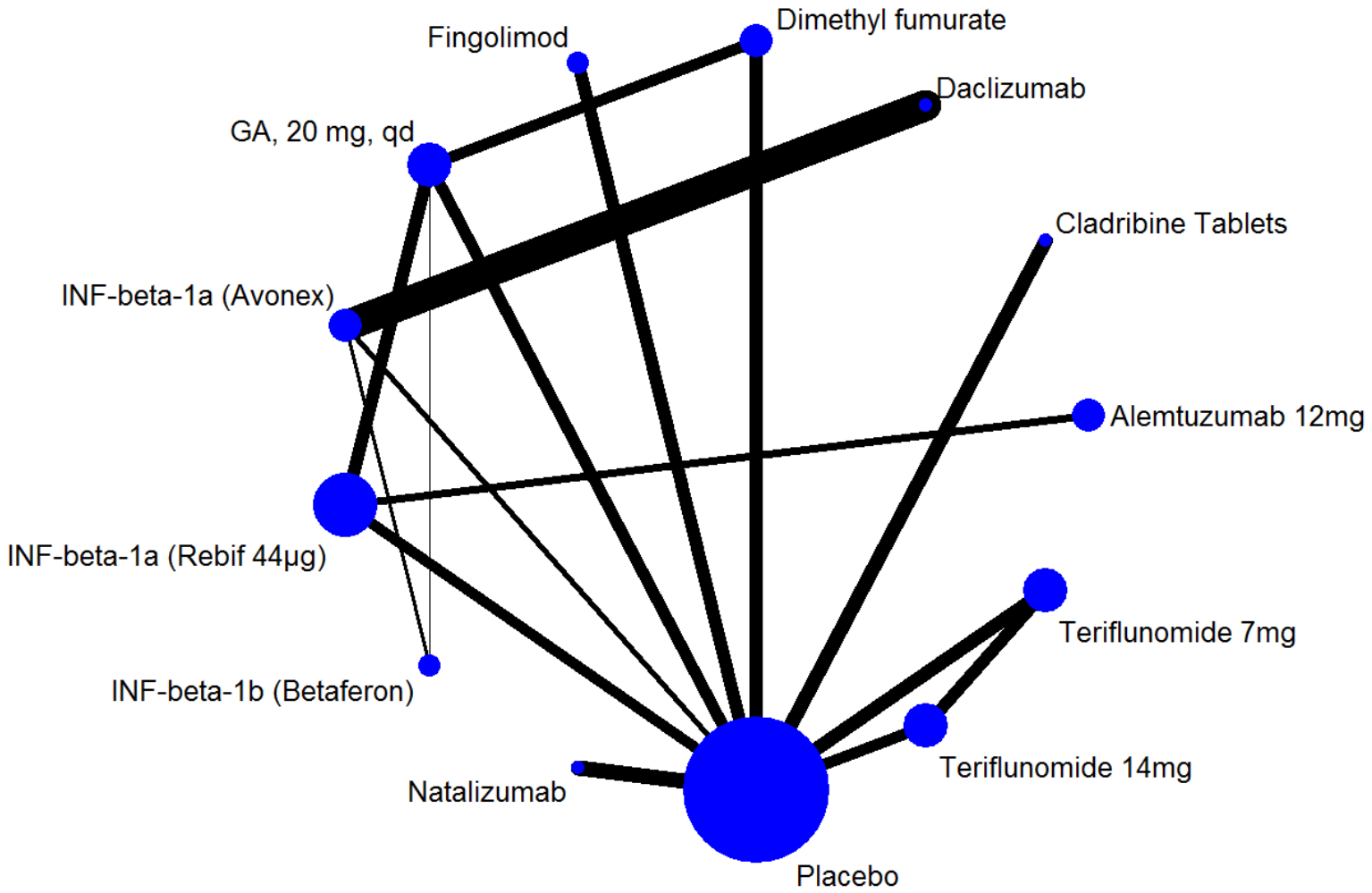

Figure 11 Network plot for the network meta-analysis of 6-month CDP at 24 months (ITT population)

*Nodes of the network plot are weighted by the number of trials the intervention is included in, edges of the network plot are weighted by the total number of participants for each pairwise comparison.
bid=twice a day; CDP=confirmed disability progression; DMF=dimethyl fumarate; GA=glatiramer acetate; µg=microgram; mg=milligram; od=once daily; qd=per day; q1w=once a week; q4w=every 4 weeks; tiw=thrice a week; INF= interferon; ITT=intention to treat;
Source: produced by the ERG, based on the numbers of Table 87

Table 88 Summary of trials used in the network meta-analysis for 6-month CDP at 24 months (HDA-RRMS subgroup)

Study	Treatment	Comparator	HR	LCI	UCI
PRISMS trial (unpublished data)	INF-β-1a (Rebif 44µg)	Placebo	0.56	0.37	0.86
CLARITY trial	Cladribine tablets	Placebo	0.18	0.08	0.44
CARE-MS I trial	Alemtuzumab, 12mg, qd	INF-β-1a (Rebif 44µg)	0.83	0.40	1.88

CDP=confirmed disability progression; µg=microgram; qd=per day; HDA-RRMS= high disease activity relapsing remitting multiple sclerosis; HR=hazard ratio; INF- β= interferon-beta; LCI=lower bound of 95% confidence interval; UCI=upper bound of 95% confidence interval
Source: Table A2.4, company response to ERG clarification letter

Table 89 Summary of trials used in the network meta-analysis for 6-month CDP at 24 months (RES-RRMS subgroup)

Study	Treatment 1	Events 1	Total1	Treatment 2	Events 2	Total2	Number of arms
AFFIRM trial	Placebo	16	61	Natalizumab, 300mg, q4w	15	148	2
CARE-MS II trial	Alemtuzumab, 12mg, qd	7	101	INF-β-1a (Rebif 44µg)	7	42	2
CLARITY trial	Placebo	9	41	Cladribine tablets	6	50	2
PRISMS trial (unpublished data)	Placebo	13	19	INF-β-1a (Rebif 44µg)	7	14	2

CDP=confirmed disability progression; mg=milligram; µg=microgram od=once daily; qd=per day; q4w=every 4 weeks; RES-RRMS=rapidly evolving severe relapsing remitting multiple sclerosis;
Source: Table A4.4, company response to ERG clarification letter

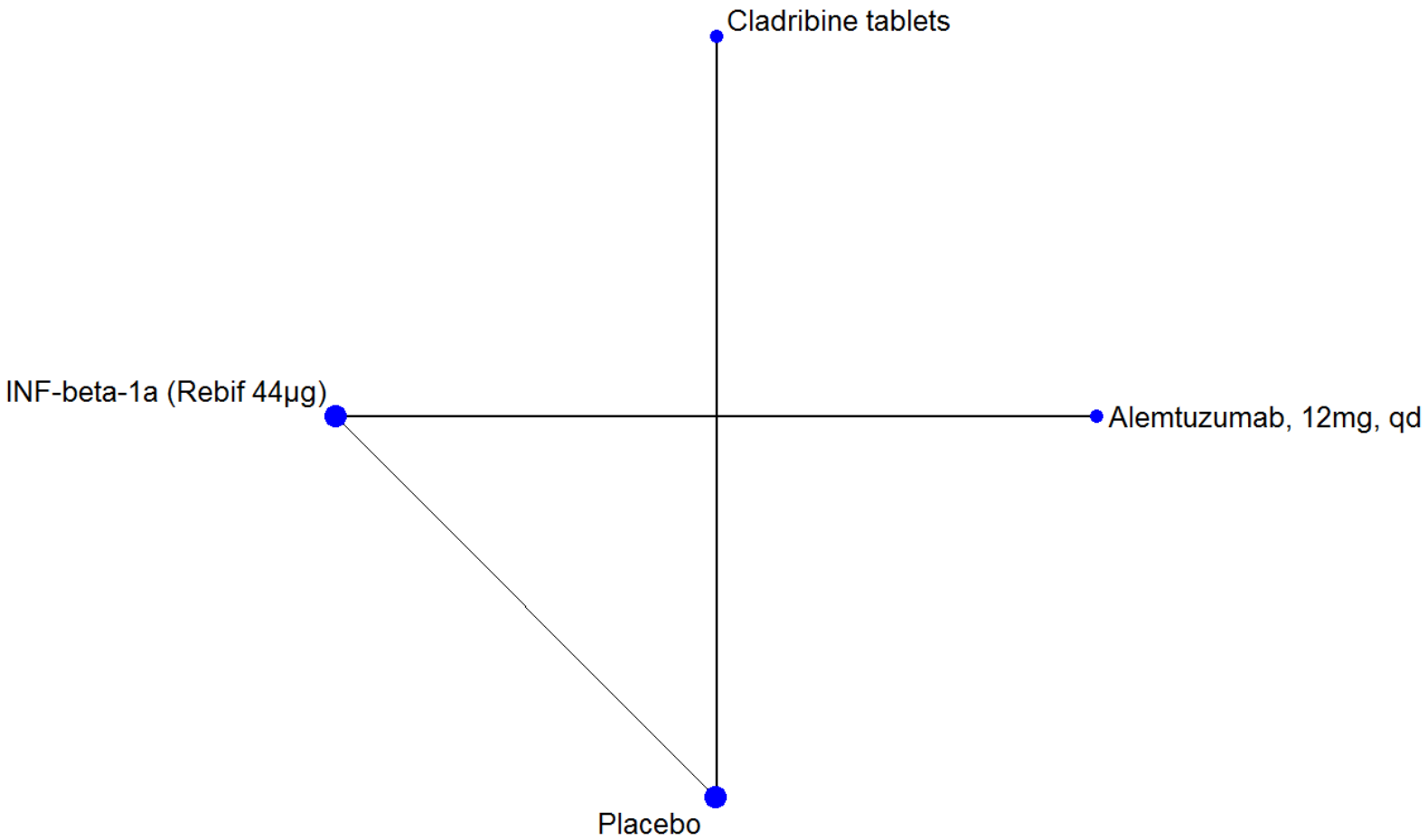

Figure 12 Network plot for the network meta-analysis of 6-month CDP at 24 months (HDA-RRMS subgroup)

*Nodes of the network plot are weighted by the number of trials the intervention is included in, edges of the network plot are weighted by the standard error of the HR for each pairwise comparison.
CDP=confirmed disability progression; µg=microgram; qd=per day; HDA-RRMS= high disease activity relapsing remitting multiple sclerosis; HR=hazard ratio; INF= interferon;
Source: produced by the ERG, based on the numbers of Table 88

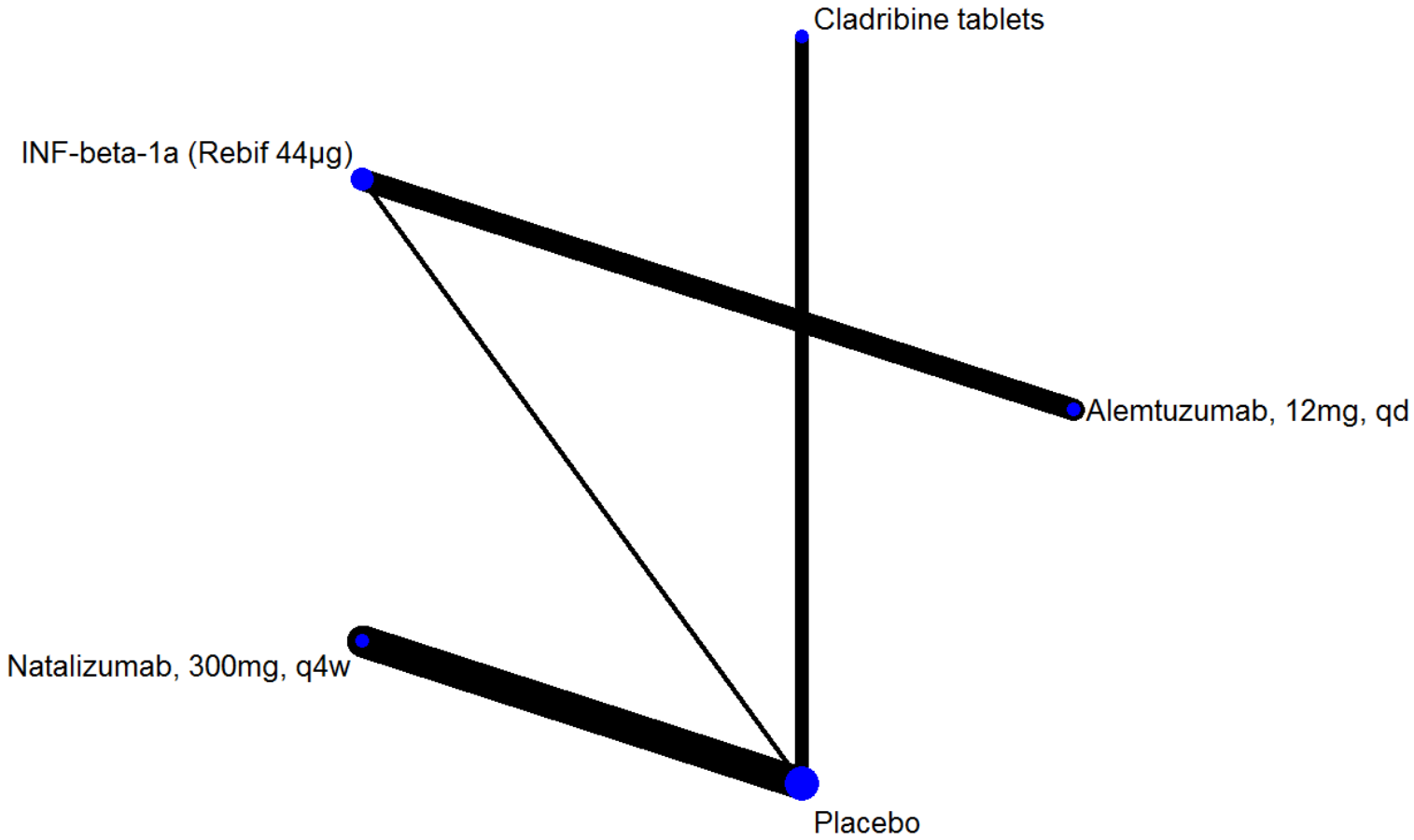

Figure 13 Network plot for the network meta-analysis of 6-month CDP at 24 months (RES-RRMS subgroup)

*Nodes of the network plot are weighted by the number of trials the intervention is included in, edges of the network plot are weighted by the total number of participants for each pairwise comparison.
CDP=confirmed disability progression; mg=milligram; µg=microgram od=once daily; qd=per day; q4w=every 4 weeks; RES-RRMS=rapidly evolving severe relapsing remitting multiple sclerosis;
Source: produced by the ERG, based on the numbers of Table 89

10.3 Sensitivity analyses of key efficacy outcomes

The company conducted sensitivity analyses to evaluate the impact of study characteristics on the results of the base-case NMA. Sensitivity analyses were conducted based on following parameters where applicable:

- Diagnostic criteria: Sensitivity analysis was conducted after excluding studies utilizing Poser diagnostic criteria and studies for which diagnostic criteria was unclear
- Year of publication: Sensitivity analysis was conducted after excluding studies published prior to the year 2000
- Blinding: Sensitivity analysis was conducted after excluding open-label studies and studies for which blinding status was unclear
- Study phase: Sensitivity analysis was conducted after excluding phase II studies

Results of these sensitivity analyses for key efficacy outcomes (ARR, 3-month CDP at 24 months and 6-month CDP at 24 months) are presented in this section. Results of sensitivity analyses for the proportion of participants relapse-free at 12 and 24 months and for tolerability outcomes (all cause and AE related study withdrawals and treatment withdrawals) are presented in Appendix B of the company response to the ERG clarification letter.

For ARR, there was no change in the direction of the relative treatment difference between cladribine tablets and comparators, however, alemtuzumab 12mg qd which presented numerically favourable results compared to cladribine tablets in the original analysis was significantly favourable after sensitivity analysis based on diagnostic criteria (Table 90). The company reason that this difference is due to sensitivity analysis with a lower number of studies, indicating reduced power to detect the difference.

For both 3-month CDP at 24 months and 6-month CDP at 24 months, the treatment difference versus placebo, which was significantly favouring cladribine tablets in the original analysis was no longer significant in the sensitivity analyses of diagnostic criteria and publication year. All other results of sensitivity analyses were in line with the base-case results.

Table 90 Summary of sensitivity analysis results for ARR in the ITT population (rate ratio and 95% CrI)

Comparator	Base-case results	Diagnostic criteria	Study phase	Blinding status	Year of publication
Placebo	0.42 (0.32, 0.54)	0.42 (0.31, 0.56)	0.42 (0.32, 0.54)	0.42 (0.32, 0.53)	0.42 (0.32, 0.54)
Alemtuzumab, 12 mg, qd	1.3 (0.93, 1.83)	1.48 (1, 2.3)	1.33 (0.96, 1.87)	1.34 (0.98, 1.85)	1.28 (0.89, 1.84)
Daclizumab HYP, 150 mg, q4w	0.92 (0.66, 1.25)	0.89 (0.62, 1.3)	0.89 (0.64, 1.23)	0.93 (0.69, 1.24)	0.91 (0.65, 1.26)
DMF, 240 mg, bid	0.78 (0.57, 1.07)	0.78 (0.54, 1.12)	0.78 (0.56, 1.05)	0.79 (0.58, 1.04)	0.78 (0.56, 1.08)
Fingolimod, 0.5 mg, qd	0.91 (0.67, 1.22)	0.91 (0.65, 1.26)	0.9 (0.66, 1.26)	0.9 (0.69, 1.19)	0.9 (0.67, 1.22)
GA, 20 mg, qd	0.64 (0.48, 0.85)	0.61 (0.43, 0.85)	0.61 (0.46, 0.83)	0.64 (0.48, 0.81)	0.61 (0.45, 0.83)
GA, 40mg, tiw	0.62 (0.44, 0.87)	0.63 (0.42, 0.92)	0.62 (0.45, 0.88)	0.63 (0.45, 0.86)	0.63 (0.44, 0.87)
IFN beta-1a, 22 mcg, tiw	0.58 (0.42, 0.81)	-	0.59 (0.43, 0.81)	0.57 (0.43, 0.77)	-
IFN beta-1a, 30 mcg, q1w	0.52 (0.39, 0.68)	0.5 (0.36, 0.7)	0.5 (0.38, 0.67)	0.53 (0.4, 0.68)	0.51 (0.38, 0.69)
IFN beta-1a, 44 mcg, tiw	0.63 (0.47, 0.84)	0.67 (0.47, 0.99)	0.64 (0.48, 0.86)	0.61 (0.47, 0.8)	0.62 (0.45, 0.85)
IFN beta-1b, 250 mcg, eod	0.62 (0.47, 0.83)	0.57 (0.38, 0.88)	0.6 (0.44, 0.82)	0.6 (0.45, 0.78)	0.6 (0.43, 0.83)
Natalizumab, 300 mg, q4w	1.22 (0.89, 1.68)	1.24 (0.86, 1.8)	1.21 (0.88, 1.67)	1.21 (0.91, 1.64)	1.23 (0.89, 1.71)
PEG IFN beta-1a, 125 mcg, q2w	0.64 (0.44, 0.92)	0.64 (0.42, 0.97)	0.63 (0.44, 0.91)	0.62 (0.45, 0.9)	0.64 (0.44, 0.95)
Teriflunomide, 14 mg, od	0.62 (0.46, 0.84)	0.63 (0.45, 0.88)	0.63 (0.47, 0.84)	0.63 (0.47, 0.84)	0.63 (0.46, 0.84)
Teriflunomide, 7 mg, od	0.54 (0.4, 0.72)	0.54 (0.38, 0.75)	0.54 (0.4, 0.72)	0.58 (0.43, 0.75)	0.54 (0.4, 0.72)

Green highlighted cells represent statistically significant results in favour of cladribine tablets; Red highlighted cells represent statistically significant results in favour of comparator; "-" indicates that NMA was not feasible against these interventions, either due to lack of connections within the networks or due to lack of studies

ARR=annualised relapse rate; bid=twice a day; DMF=dimethyl fumarate; EOD=every other day; GA=glatiramer acetate; HYP=high yield process; IFN=interferon; mcg=microgram; mg=milligram; od=once daily; PEG=pegylated; qd=per day; q1w=once a week; q2w=every 2 weeks; q4w=every 4 weeks; qw=once weekly; tiw=thrice a week
Source: Table 13, Appendix B, company response to ERG clarification letter

Table 91 Summary of sensitivity analysis results for 3-month CDP at 24 months in the ITT population (hazard ratio and 95% CrI)

Comparator	Base-case results	Diagnostic criteria	Study phase	Year of publication
Placebo	0.6 (0.38, 0.95)	0.61 (0.34, 1.06)	0.6 (0.38, 0.95)	0.61 (0.34, 1.06)
Alemtuzumab, 12 mg, qd	2.25 (0.81, 6.49)	-	-	-
Daclizumab HYP, 150 mg, q4w	0.92 (0.41, 2.04)	0.93 (0.35, 2.46)	0.92 (0.42, 2.01)	0.93 (0.35, 2.46)
DMF, 240 mg, bid	0.94 (0.54, 1.66)	0.91 (0.45, 1.81)	0.93 (0.53, 1.64)	0.91 (0.45, 1.81)
Fingolimod, 0.5 mg, qd	0.78 (0.45, 1.35)	0.78 (0.39, 1.54)	0.77 (0.45, 1.35)	0.78 (0.39, 1.54)
GA, 20 mg, qd	0.84 (0.49, 1.47)	0.71 (0.32, 1.54)	0.8 (0.46, 1.39)	0.71 (0.32, 1.54)
IFN beta-1a, 22 mcg, tiw	0.91 (0.47, 1.79)	0.78 (0.35, 1.78)	0.91 (0.47, 1.76)	-
IFN beta-1a, 30 mcg, q1w	0.78 (0.39, 1.54)	0.78 (0.35, 1.78)	0.78 (0.4, 1.53)	0.78 (0.35, 1.78)
IFN beta-1a, 44 mcg, tiw	0.93 (0.47, 1.83)	-	0.92 (0.47, 1.81)	-
IFN beta-1b, 250 mcg, eod	0.68 (0.39, 1.26)	0.51 (0.2, 1.3)	0.66 (0.37, 1.21)	0.51 (0.2, 1.3)
Natalizumab, 300 mg, q4w	1.1 (0.58, 2.07)	1.1 (0.5, 2.41)	1.1 (0.59, 2.05)	1.1 (0.5, 2.41)
Teriflunomide, 14 mg, od	0.82 (0.47, 1.43)	0.82 (0.41, 1.63)	0.82 (0.47, 1.43)	0.82 (0.41, 1.63)
Teriflunomide, 7 mg, od	0.67 (0.38, 1.16)	0.67 (0.33, 1.31)	0.66 (0.38, 1.15)	0.67 (0.33, 1.31)

Green highlighted cells represent statistically significant results in favour of cladribine tablets; "-" indicates that NMA was not feasible against these interventions, either due to lack of connections within the networks or due to lack of studies.
Sensitivity analysis of blinding was not conducted due to lack of studies contributing to the network which were open-label or had unclear methods of blinding.

bid=twice a day; CDP=confirmed disability progression; DMF=dimethyl fumarate; GA=glatiramer acetate; IFN=interferon; mcg=microgram; mg=milligram; od=once daily; qd=per day; q1w=once a week; q4w=every 4 weeks; qw=once weekly; tiw=thrice a week
Source: Table 14, Appendix B, company response to ERG clarification letter

Table 92 Summary of sensitivity analysis results for 6-month CDP at 24 months in the ITT population (hazard ratio and 95% CrI)

Comparator	Base-case results	Diagnostic criteria	Study phase	Blinding status	Year of publication
Placebo	0.54 (0.29, 0.99)	0.54 (0.28, 1.03)	0.54 (0.33, 0.88)	0.54 (0.31, 0.94)	0.54 (0.29, 1)
Alemtuzumab, 12 mg, qd	1.37 (0.58, 3.32)	0.81 (0.25, 2.93)	0.52 (0.25, 1.08)	0.61 (0.28, 1.43)	0.86 (0.28, 2.97)
Daclizumab HYP, 150 mg, q4w	1.07 (0.42, 2.65)	0.97 (0.32, 3.01)	1.12 (0.52, 2.37)	1.11 (0.47, 2.61)	0.91 (0.31, 2.51)
DMF, 240 mg, bid	0.85 (0.41, 1.81)	0.8 (0.36, 1.8)	0.77 (0.42, 1.43)	0.77 (0.39, 1.55)	0.81 (0.38, 1.76)
Fingolimod, 0.5 mg, qd	0.79 (0.37, 1.64)	0.79 (0.35, 1.73)	0.79 (0.43, 1.43)	0.79 (0.4, 1.54)	0.79 (0.37, 1.66)
GA, 20 mg, qd	0.81 (0.37, 1.73)	0.62 (0.25, 1.53)	0.55 (0.29, 1.03)	0.54 (0.27, 1.12)	0.65 (0.29, 1.57)
IFN beta-1a, 30 mcg, q1w	0.79 (0.37, 1.64)	0.72 (0.28, 1.85)	0.82 (0.44, 1.52)	0.82 (0.41, 1.64)	0.67 (0.27, 1.57)
IFN beta-1a, 44 mcg, tiw	0.76 (0.35, 1.61)	0.46 (0.14, 1.42)	0.34 (0.19, 0.64)	0.34 (0.17, 0.7)	0.48 (0.17, 1.46)
IFN beta-1b, 250 mcg, eod	1.79 (0.65, 4.73)		0.8 (0.18, 3.77)	0.79 (0.17, 4.06)	1.47 (0.5, 4.21)
Natalizumab, 300 mg, q4w	1.21 (0.52, 2.77)	1.2 (0.49, 2.96)	1.21 (0.61, 2.38)	1.21 (0.56, 2.57)	1.21 (0.51, 2.84)
Teriflunomide, 14 mg, qd	0.66 (0.31, 1.38)	0.66 (0.3, 1.47)	0.66 (0.36, 1.22)	0.66 (0.33, 1.3)	0.66 (0.31, 1.4)
Teriflunomide, 7 mg, qd	0.57 (0.27, 1.18)	0.57 (0.25, 1.25)	0.57 (0.31, 1.04)	0.56 (0.29, 1.11)	0.57 (0.26, 1.2)

Green highlighted cells represent statistically significant results in favour of cladribine tablets; "-" indicates that NMA was not feasible against these interventions, either due to lack of connections within the networks or due to lack of studies.

bid=twice a day; CDP=confirmed disability progression; eod=every other day; DMF=dimethyl fumarate; GA=glatiramer acetate; IFN=interferon; mcg=microgram; mg=milligram; od=once daily; qd=per day; q1w=once a week; q4w=every 4 weeks; qw=once weekly; tiw=thrice a week
Source: Table 15, Appendix B, company response to ERG clarification letter

10.4 Assessment of risk of bias in the trials included in the network meta-analysis

The company performed an assessment of study quality and risk of bias using the NICE checklist[31] for all trials included in the NMAs. Detailed information for each domain of quality can be found in Appendix D.1.1.3 and Appendix D.1.1.4 of the CS. A summary of the risk of bias domains is also provided in Appendix 10.4 of this ERG report.

Of the 42 trials included in at least one NMA, the method of generation of random sequence number was adequate in 32 (76%); in the remaining 10 trials (24%), this information was unclear. Concealment of allocation was adequate in 34 (81%) of the included trials; in the remaining eight trials (19%), allocation concealment was unclear. Baseline characteristics within the treatment groups were judged to be comparable across the 42 included studies.

Overall, 28 (67%) of the included trials were double-blind and eight (19%) were single-blind (outcome assessors blinded). These 36 trials were judged to have a low risk of bias. One of the included trials (the REFORMS trial[89]) was open-label except for blinded assessments of injection site reactions and therefore judged to be at high risk of bias The risk of bias associated with blinding was judged to be unclear in five studies[56,90-93] where the method of blinding and/or who was blinded was unclear. The company conducted a sensitivity analysis excluding the six trials[56,89-93] that were open-label or for which blinding status was unclear, results are presented in Appendix 11.3 and Appendix B of the company response to the ERG clarification letter.

Across the 42 included trials, reasons for withdrawals were adequately reported in 36 (86%), one trial (the CARE-MS II trial[58]) was judged to be at high risk of bias as there were some unexpected imbalances in drop-outs between the treatment groups and in the remaining five trials[90,91,94-96] the number and/or reasons for withdrawals were inadequately reported. In 27 of the trials (64%), the reporting of outcomes was adequate and was associated with low risk of bias, while outcome selection and reporting were not clear in the remaining 15 (36%) trials.

All except one of the 42 included trials (98%) reported an ITT or modified ITT analysis for evaluating efficacy or safety outcomes, while the remaining trial (Calabrese 2012[90]) reported using a per-protocol approach to statistical analysis which was judged to be at high risk of bias.

10.5 ERG revisions to the company model

This appendix contains details of the changes that the ERG made to the company model. To generate results for the RES-RRMS subgoup, the population in the "Settings" sheet of the company model needs to be set to "RES". Similarly, to generate results for the SOT-RRMS subgroup, the population in the "Settings" sheet of the company model needs to be set to "SOT".

ERG revisions	Implementation instructions
RES-RRMS ONLY R1a) For 6-month CDP, cladribine tablets have no effectiveness compared to placebo. For qualifying ARR, the effectiveness of alemtuzumab, and daclizumab is set equal to the effectiveness of cladribine tablets	In Sheet "Clinical – treatment effect" Copy cell L43 In range L43:L47 Paste values In cell U44 set value = 0.31 In cell U47 set value = 0.31 In cell N34 set value = NMA
RES-RRMS ONLY R1b) For qualifying ARR, the effectiveness of alemtuzumab and daclizumab is set equal to the effectiveness of cladribine tablets. For 6-month CDP, the effectiveness of alemtuzumab, natalizumab and daclizumab is set equal to the effectiveness of cladribine tablets	In Sheet "Clinical – treatment effect" Copy range L43:L47 In range L43:L47 Paste values In cell L48 set value = 1.000 In cell U44 set value = 0.31 In cell U47 set value = 0.31 In cell N34 set value = NMA
SOT-RRMS ONLY R1) For qualifying ARR and 6-motnh CDP, the effectiveness of alemtuzumab, fongolinod and daclizumab is set equal to the effectiveness of cladribine tablets	In Sheet "Clinical – treatment effect" Copy cell L43 In range L43:L47 Paste values In cell U44 set value = 0.48 In cell U45 set value = 0.48 In cell N34 set value = NMA

ERG revisions	Implementation instructions
R2) Waning effect: the effectiveness of cladribine tablets is set to 75% between years 2 and 4	In Sheet “Costs - drug” In range “AB9:AE10” set values = 0
R3) No re-exposure to cladribine or alemtuzumab	In Sheet “Clinical – treatment effect” In cell P76 set value = 0.75 In cell T76 set value = 0.75
R4) Treatment discontinuation only at EDSS state 7 after 2 years	In Sheet “Clinical – treatment persistence” In range “R47:R49” set values = 0 In range “W47:W49” set values = 0
R5) TA32 EDSS state costs	In Sheet “Costs - disease” In cell P27 set value = No cost In cell K30 set value = £949 In cell K31 set value = £987 In cell K32 set value = £724 In cell K33 set value = £3958 In cell K34 set value = £1917 In cell K35 set value = £3253 In cell K36 set value = £4342 In cell K37 set value = £11429 In cell K38 set value = £27838 In cell K39 set value = £22274
R6) No carer disutility	In Sheet “Health utility” In cell K46 set value = No
R7) 2-year time horizon	In sheet “Settings” In cell K10 set value = 2
R8) 4-year time horizon	In sheet “Settings” In cell K10 set value = 4